PHARMACOLOGICAL EVALUATION OF METHANOLIC EXTRACT OF LEAVES OF *ARTOCARPUS HIRSUTUS* LAM.

Dissertation submitted to

The Tamilnadu Dr. M.G.R. Medical University

Chennai - 600 032

In partial fulfillment for the degree of

MASTER OF PHARMACY

IN

PHARMACOLOGY

By

Reg. No: 261225153

DEPARTMENT OF PHARMACOLOGY

PERIYAR COLLEGE OF PHARMACEUTICAL SCIENCES

TIRUCHIRAPPALLI - 620 021

(An ISO 9001:2008 Certified Institution)

APRIL - 2014

Dr. S. Karpagam Kumara Sundari, **M.Pharm, Ph.D.,**
Head, Department of Pharmacology
Periyar College of Pharmaceutical Sciences
Tiruchirappalli - 620 021.

CERTIFICATE

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Place : Tiruchirappalli

Date : **(Dr. S. Karpagam Kumara Sundari)**

Prof. Dr. R. Senthamarai, M.Pharm, Ph.D.,
Principal
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LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

HERBAL PLANTS

The plant kingdom is the most important treasure of the nature and it serves as the important source of drugs. Drugs of natural origin are relatively safer and even cheaper. More than 65% of total world population depend on herbal and traditional drugs. The science of herbal and traditional drugs has been evolved along with the civilization. As the scientific knowledge accumulated, human beings have started deviating from the usage of herbal drugs to drugs of synthetic origin. All these drugs of synthetic origin are chemical molecules and when they are administered to human, they react with one or other endogenous substance to elicit their response. But along with the correction of the pathophysiological conditions these drug molecules also produce adverse reactions by interacting with other endogenous substances[1].

Status of Herbal Medicine in India

India has rich tradition of herbal medicine as evident from Ayurvedic, which could not have flourished for two thousand years without any scientific basis. Ayurveda which literally means Knowledge (Veda) of life (Ayur) had its beginning in Atharvaveda (Circa 1500-1000 BC). Vegetable products dominated Indian Materia Medica which made extensive use of bark, leaves, flower, fruit, root, tubers and juices. Charak, Sushruta and Vagbhata described 700 herbal drugs with their properties and clinical effects. Based on clinical effects 50 categories of drugs have been described such as appetizers, digestive stimulant, laxatives, antidiarrhoea, antihaemorrhoid, antiemetic, antipyretic, antiinflammatory, antipruritic, antiasthmatic, antiepileptic, antihelminthic, haemopoeitic, haemostatic, analgesic, sedative, promoter of strength, complexion, voice, increases the sperm count, breast milk secretion, fracture and wound healing and destroyer of kidney stones[2].

Throughout the history from the Bible, Koran, Vedas and other old texts, the medicinal benefits of herbs are quoted.

Herbs have a variety of uses including Culinary, Medicinal or in some cases even spiritual usage.

General usage differs between culinary herbs and Medicinal herbs. In medicinal or spiritual use any of the parts of the plant might be considered herbs, including leaves, roots, flowers, seeds, resin, root bark, inner bark, berries and sometimes the pericarp or other portions of the plants. A great deal of research is currently being focused worldwide on various herbs and traditional medicine in the hope that new cures for illness and disease can be found. In the early 19^{th} century when chemical analysis first became available, scientists began to extract and modify the active ingredients from plants. Often herbs may be used together because the combination is more effective and may have fewer side effects.

Plant Constituents

The plant may be considered as a biosynthetic laboratory, not only for the chemical compounds such as carbohydrates, proteins and lipids that are utilized as food by man, but also for a multiple of compounds like glycosides, alkaloids, volatile oils, tannins, etc., that exert a physiological effect. The compounds that are responsible for therapeutic effect are usually the secondary metabolites. A systemic study of a crude drug embraces through consideration of both primary and secondary metabolites derived as a result of plant metabolism.

Traditional Herbal Medicine (THM)

THM is a practice of protecting and restoring health that existed before the relatively recent arrival of modern medicine. According to WHO, up to 80% of people living in developing countries still rely primarily on traditional medicine for their healthcare.

Traditional Unani Medicine (TUM)

TUM originated in ancient Greece around 400BC. Hippocrates, also known as the founder of allopathic medicine, is considered to be first unani physician. Unani treatments for restoring equilibrium and normal body functions involve the prescribing of herbal and mineral medicines, a specific diet.

Traditional AyurvedicMedicine(TAM)

TAM originated in India around 5000 BC with the publications of "Rigveda" and "Atharvanaveda" that contain hymns on disease and herbal treatments. The term Ayurveda means "Science of Life" a medicinal science where in health is achieved body-mind matrix usually involve the prescribing of herbal medicines, specific diet and physical activity routines, among other therapies including massage and various purification treatments.

PLANTS AS LEADS TO DISCOVERY OF NEW DRUGS

Based on the strong and traditional knowledge based on the use of plants, as therapeutic agents rational approach is being developed to use medicinal plants as a lead for the discovery of active molecules. Established drugs are also used as leads to synthesize new derivatives, which led to the well known category of drugs. They are also termed as molecular manipulations or molecules roulette of existing drugs.

HERBAL MEDICINE TODAY

The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous peoples traditional medicine and a common element in ayurvedic, homeopathic, naturopathic, traditional, oriental, and Native American Indian medicine. WHO notes that of 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value.

Today, the U.S. Pharmacopoeia, with its reliance on herbal compounds, has been all but forgotten. Most modern physicians rely on the Physician's Desk Reference, an extensive listing of chemically manufactured drugs. It is important to note that each entry in this enormous volume, in addition to specifying the chemical compound and actions of a particular drug, also includes an extensive list of contraindications and possible side effects.

Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, and other problems. For example ephedra is a herb used in Traditional Chinese Medicine for more than two thousand years to treat asthma and other respiratory problems. Ephedrine the active ingredient in ephedra, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems. It helps the patient to breath more easily.

Why People Use Herbal Medicine?

Herbal medicines is now being used by an increasing number of patients who typically do not report to their clinicians concomitant use[3]. Patients use home remedies for acute, often self limiting conditions, such as cold, sore throat, or bee sting, it is often because professional care is not immediately available, too inconvenient, costly or time-consuming. In rural areas, there are additional cultural factors that encourage the use of botanicals, such as the environment and culture, a "man earth relationship". People believe that where an area gives rise to particular disease, it will also support plants that can be used to cure it[4].

Difference of Herbal and Conventional Drugs[5]

Although superficially similar, herbal medicine and conventional pharmacotherapy have three important differences.

Use of Whole plant - Herbalists generally use unpurified plant extracts containing several different constituents. It is claimed that these can work together than the summed effects of its components. It is also claimed that toxicity is reduced when whole herbs are used instead of isolated active ingredients

Combined Herbs-several different herbs are used together, practitioners say that the principles of synergy and buffering apply to combinations of plants and claim that combining herbs improves efficacy and reduces adverse effect. Herbal practitioners use different diagnostic principles from conventional practitioners. For e.g., when treating arthritis, they might observe, "that the arthritis results from "an accumulation of metabolic waste products"

Biodiversity of Medicinal and Aromatic Plants

Because of so many reasons biodiversity of medicinal and aromatic plants is affected . India has 2.4% of world's area with 8% of global bio-diversity. It is one of the 12 mega-diversity hot-spot regions of the world, other countries being Brazil, Colombia,China, South Africa, Mexico, Venezuela, Indonesia, Ecuador, Peru, USA and Bolivia. Across the country, the forests of India are estimated to harbour 90% of India's medicinal plants diversity in the wide range of forest types that occur. Only about 10% of the known medicinal plants of India are restricted to non-forest habitats. The estimated numbers of plant species and those used for medicinal purpose vary. According to Schippmann *et al*. one fifth of all the plants found in India are used for medicinal purpose. The world average stands at 12.5% while India has 20% plant species of medicinal herbs[6].

But according to Hamilton (2003), India has about 44% of flora, which is used medicinally. Although it is difficult to estimate the number of medicinal and aromatic plants present worldwide, the fact remains true that India with rich biodiversity ranks first in percent flora, which contains active medicinal ingredient[7].

Table No.1: Numerical of Plants used medicinally worldwide

Country	Plant species	Medicinal plant species	%
China	26.092	4941	18.9
India	15000	3000	20
Indonesia	22500	1000	4.4
Malaysia	15500	1200	7.7
Nepal	6973	700	10
Pakistan	4950	300	6.1
Philippines	8931	850	9.5
Srilanka	3314	550	16.6
Thailand	11625	1800	15.5
USA	21641	2584	11.8
Vietnam	10500	1800	17.1
Average	13366	1700	12.5
World	422000	52885	10

The existence of traditional medicine depends on plant species diversity and the related knowledge of their use as herbal medicine. In addition both plant species and traditional knowledge are important to the herbal medicine trade and the pharmaceutical industry where by plants provide raw materials and the traditional knowledge prerequisite information[8].

India has one of the richest plant medical traditions in the world. It is a tradition that is of remarkable contemporary relevance for ensuring health security to the teeming millions. There are estimated to be around 25,000 effective plant-based formulations, used in folk medicine and known to rural communities in India. There are over 1.5 million practitioners of traditional medicinal system using medicinal plants in preventive, promotional and curative applications.

It is estimated that there are over 7800 medicinal drug-manufacturing units in India, which consume about 2000 tonnes of herbs annually[9].

Chinese herbal medicines constitute multibillion dollar industries worldwide and more than 1500 herbals are sold as dietary supplements or ethnic traditional medicines[10,11].

Another example of the use of an herbal preparation in modern medicine is the foxglove plant. This herb had been in use since 1775. At present, the millions of heart patients know the powdered leaf of this plant as the cardiac stimulant, digitalis. There are over 750,000 plants on earth. Relatively speaking, only a very few of the healing herbs have been studied scientifically.

Because modern pharmacology looks for one active ingredient and seeks to isolate it to the exclusion of all the others, most of the research that is done on plants continues to focus on identifying and isolating active ingredients, rather than studying the medicinal properties of whole plants. Herbalists, however, consider that the power of a plant lies in the interaction of all its ingredients. Plants used as medicines offer synergistic interactions between ingredients both known and unknown[12].

GASTROPROTECTIVE EFFECT

Gastrointestinal disorders are one of the severe classes of human ailments causing maximum discomfort, morbidity and mortality. Peptic ulcer is one such gut disorder. Peptic ulcer is a benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to acid and pepsin. There are several causes including, stress, alcohol consumption, cigarette smoking, H. pylori infection, ingestion of drugs and chemicals. Especially consumption of alcohol for a prolonged period, smoking of cigarettes, or chronic consumption of NSAIDs are causing peptic ulcers. The role of free radicals in the pathogenesis of peptic ulcer due to mucosal damage is established. The symptoms of peptic ulcer are severe pain and irritation in the upper abdomen. If it is not treated properly, it may results in perforations in the wall of the gastrointestinal tract.

Therefore, normally chronic dietary control and pharmacotherapeutic management is adopted for treating peptic ulcer[13].

Several classes of drugs like anti-histamines (H_2-blockers), proton pump inhibitors (Omeprazole, lansoprazole,etc.), anticholinergic agents (pirenzipine), prostaglandins (misoprostol, euprostil), antacids (sodium bicarbonate, magnesium hydroxide gel, etc.), sucralfate, colloidal bismuth, etc., have been used for pharmacotherapeutic management of peptic ulcers. Now it is a trend to think of antioxidants in treating peptic ulcer. However no such agent is available for clinical practice. However, several side effects like arrythmias, impotence, gynaecoemastia, haematopoetic changes, etc. associated with the various synthetic drugs used in the management of peptic ulcer is restricting the chronic usage of these agents.

In addition to this the escalating cost of these drugs is making it difficult to afford and use them for a chronic period. It is also observed that during chronic usage of these agents may result in the drug-drug interactions with the concomitantly used drugs.

Peptic ulcer[13]

It is a chronic inflammatory condition involving a group of disorders characterized by ulceration in regions of upper gastrointestinal tract where pareital cells secrete pepsin and hydrochloric acid.

Signs and symptoms[13]

In peptic ulcer, patients can be asymptomatic or experience anorexia, nausea, vomiting, bleaching and blotting and heart burn or epigastric pain.

Epidemiology[13]

The life time prevalence of peptic ulcer disease is 5 to 10% in the general population. There are approx 3.9 million patients with peptic ulcer disease in United States with 200,000 to 400,000 new cases reported each year. The peak incidence is between 50 and 70 years of age.

Etiology of chronic ulceration[13]

Heredity

Patients with peptic ulcer often have a family history of the disease. This is particularly the case with duodenal ulcers, which develop below the age of 20 years.

The relatives of gastric ulcer patients have 3 times the expected number of gastric ulcer but duodenal ulcer occur with the same frequency amongst relatives as in the general population.

Acid-pepsin Vs Mucosal resistance

The immediate cause of peptic ulceration is digestion of the mucosa by acid and pepsin of the gastric juice, but the sequence of events leading to this is unknown. Digestion by acid and pepsin can't be the only factor involved, since the normal stomach is obviously capable of resisting digestion by its own secretion.The concept of ulcer aetiology may be written as "acid plus pepsin Vs mucosal resistance".

Gastric hyper secretion

Ulcers occur only in the presence of acid and pepsin they are never found in achlorhydric patients such as those with pernicious anaemia. Acid secretion is more important in the etiology of duodenal than gastric ulcer. Peptic ulcer is the most common gastrointestinal disorder in clinical practice. Considering the several side effects like Arrythmias, impotence, gynacoemastia and hematopoietic changes, of synthetic drugs, hence their usage for a chronic period is restricted. However, comparatively indigenous drugs possessing fewer side effects. Hence, the search for better alternatives for synthetic drugs is on rise.

There is evidence concerning the participation of reactive oxygen species in the etiology and pathophysiology and human disease, studies has shown alterations in the antioxidant status following ulceration indicating that free radicals, seems to be associated with the pylorus ligation and ethanol induced ulceration in rats[14].

Different factors related to acid secretion[15]

a) General factor

Vagal hormonal effect, histamine and epinephrine, insufficient circulation, shock and general ischemia increase the acid secretion. Constitutional and environmental factors i.e. sex, age, temporarily, family history, social class, geographical different and occupation may also influence the acid release and local factors in stomach.

b) Aggressive factor

HCl, pepsin, refluxed bile, NSAIDs, alcohol, pancreatic proteolytic enzymes, ingested irritants, bacterial toxins, physiochemical trauma all of these factors increase the acid secretion .

c) Digestive factors

Mucus, bicarbonates, blood flow, resolution of epithelium, the current status of drug therapy.

Cause of Ulcer

Stress[16]

Stress can arise from prolonged anxiety, tension and emotion, sever physical discomfort, hemorrhagic and surgical shocks, burns and trauma, thereby resulting in sever gastric ulceration.

The mechanism of gastric ulceration is poorly understood. Recently research has shown that restraint cold stress causes severe haemorrhagic ulcer through dearrangement of the mucosal antioxidant enzymes such as superoxide dismutase and peroxides. This is the stress condition arising mainly from physiological discomfort and the mechanism of ulceration caused in this case should be different from ulcer caused due to other factors.

The stress generate highly reactive OH^- radicals that causes oxidative damage of the gastric mucosa and that the radical is formed by metal catalysed. Harberweiss reaction betweenO_2^- and H_2O_2 following induction of the superoxide dismutase and oxidative damage of gastric peroxidase.

Alcohol[17]

Alcohol causes secretion of gastric juice and decrease mucosal resistance. Protein content of gastric juice is significantly increased by ethanol. This could be due to leakage of plasma proteins in to the gastric juice with weakening of mucosal resistance barrier of gastric mucosa. This leads to peptic ulcer.

H. Pylori[18]

It is a gram negative bacteria found in gastric and duodenal mucosa of most persons particularly the elderly. Bacteria, while in the mucosa, split urea into ammonia and thus elevates the local pH, damage of local region of the mucosa by high alkalinity. In this way they strongly help the peptic ulcer development.

Treatment of ulcer

Antibiotics[18]

For the eradication of H. Pylori antibiotics like

- Amoxicillin
- Clarithromycin
- Metronidazole and some time colloidal bismuth sub citrate has been used

Tricyclic antidepressant[18]

On theoretical grounds, tricyclic antidepressants should be helpful in treatment of peptic ulcers, few desirable like amitryptiline can block both Ach. and H_2 receptors.

Proton pump inhibitors[18]

Omeprazole, Lansaprazole are the two drugs belonging to the class of proton pump inhibitors omeprazole is prototype. H^+ ion produced from HOH is pumped into canaliculus within the pareital cell by H^+ K^+ ATPase. Therefore, would result in no pumping of H^+ into the canaliculus (where it unites with Cl^- ion to form Hcl).

There will be no Hcl formed. Thus complete inhibition of proton pump must inhibit all Hcl formation omeprazole binds with H^+K^+ ATPase and inhibits the H^+K^+ ATPase i.e. abolition of Hcl formation.

Omeprazole (Chemically a benzimidazole sulfonamide) is a prodrug. It diffuses across the pareital cell eventually it is protonated.

Somatostatin analogue[18]

Octreotide is a somatostatin analogue. It has been used chiefly against the hormone secreting tumors of GIT.

Carbenoxolone[18]

It is a derivative glycyrrhic acid (obtained from liquorice) It causes increased

1) Secretion of gastric mucus.
2) Increased life span of epithelial cells of the stomach and cytoprotective action.

Antacids[18]

Major antacids are

- Aluminum compounds
- Magnesium compounds
- Calcium carbonate and
- Sodium bicarbonate

Mechanism of action

Antacids which are weak bases react with the HCl of the stomach to produce a salt plus water (thus removing HCl) raising the pH of gastric content, causing loss of peptic activity, blunting of aggressive factor.

Two types of antacids

1) Systemic

This antacids are absorbed in fair extent by the GIT to produce systemic effect.Thus $NaHCO_3$ in good deal absorbed and many cans sodium overload syndrome. Thus these antacids are not favoured now a day.

2) Non-systemic antacids

These are not absorbed or only slightly absorbed by the GIT. However the daily dose of antacids are heavy, even the so called non systemic antacids.

H_2-receptor antagonist[19]

Cimitidine was first histamine H_2-receptor antagonist available for clinical use. Ranitidine and famotidine are also act as H_2-receptor antagonist like cemetidine. They are used as ulcer healing drugs.Cimitidine is a prototype, it reduces stimulated acid and pepsin by competitive antagonism of the action of histamine on H_2-receptor.

Prostaglandin analogoues MISOPROSTOL[15]

Prostaglandin (PGE_2 and PGI_2) are major prostaglandin synthesized by the gastric mucosa.

The inhibit acid production by binding to EP_3 receptor on pareital cell prostaglandins binding to the receptor result in inhibition of adenyl cylase and decreased levels of intracellular cAMP. PGE also can present gastric injury by it is so called cytoprotective effect which include stimulating of secretion of mucin and bicarbonate and improvement in mucosal blood flow.

Coating agents

Sucralfate and colloidal bismuth, compounds are coating agents. But sucralfatein an almost pure coating agent. They form a coat selectively on the upper (rather the crater) so that acid pepsin mixture can't come in contact with the ulcer.Though formation of a coat over the ulcer is the fundamental mechanism of action of sucralfate, it acts by other mechanism also. Thus, in addition it binds with bile salt's and also stimulate PGE secretion from gastric mucosa.

Antichloinergic drugs[20]

Pareital cells contain Ach. receptors vagal stimulation leads to gastric juice secretion. Vagal stimulation plays important part in cephalic and gastric phase of secretion. The ach receptor on the pareital cells are muscarinic (to be precise M_1) receptors. This means antimuscarinic in particular pirenzepine an M_1 antagonistic, should be effective in peptic ulcer.

Table No. 2:

List of Antiulcerogenic, Anti Secretory and Gastroprotective compounds.

S.No	Established drugs	Examples
1)	Anticholinergic	Pirenzipine, Telenzipine
2)	H_2 receptor blocker	Cimetidine, Ranitidine, Famotidine
3)	Proton pump inhibitors	Omeprazole, Lansaprazole
4)	Prostaglandins	Misoporstol, Enprostil
5)	Antacids	$NaHCo_3$, MgOH.
6)	Coating agent	Sucralfate
7)	Tricyclic anti depressant	Amitryptiline
8)	Somatostatin analogue	Octreotide

Antiulcer activity of medicinal plants

a) *Turnera ulmifolia*(*Turneraceae*)[21]

b) *Asprisphmium cordatum*[22]

c) *Croton cajucara*[23]

d) Leaves of *Mikania cordata*[24]

e) Stem of *Haldinia cordifolia*[25]

f) Roots of *Tephrosia purpurea*[26]

g) Leaves of *Ziziphus jujuba* Lam [27]

h) Fruit extract of *Aegle marmelos*[28]

EPILEPSY

Neuroleptic disorders are one of the major problems in world. The word *Epilepsy* is derived from the Greek verb epilamvanein meaning to be seized, to be taken hold of orto be attacked. This terminology is derived from even older notion that all diseases represented attacks by the Gods or evil spirits, usually as punishment. By the fifth century BC, the world had gradually acquired the specific and particular meaning associated with epilepsy today.The word epilepsy is also known from the Greek as *epilepsia*, which inturn can be broken into *epi-* (upon) and *lepsis* (to take hold of, or seizure) In the past, epilepsy was associated with religious experiences and even demonic possession. In ancient times, epilepsy was known as the "Sacred Disease" because people thought that epileptic seizures were a form of attack by demons, or that the visions experienced by persons with epilepsy were sent by the Gods.

The term convulsive disorders, seizure disorder and cerebral seizures are synonymous with epilepsy they all refer to recurrent paroxysmal episodes of brain dysfunction manifested by stereotyped alterations in behavior.

Seizures can be “nonepileptic”when evoked in a normal brain by treatments such as electroshock or chemical convulsants and “epileptic” when occurring without evident provocation. Epilepsy is a neurological condition that makes people susceptible to seizures.

Epilepsy is a group of chronic neurological disorders characterized by sporadic episodes of convulsive seizures, sensory disturbance, abnormal behaviour and loss of consciousness or all of these symptoms resulting from a brain dysfunction or anabnormal discharge of cerebral neurons. [29,30]

Seizures

A seizure is a sudden, uncontrolled disturbance of the central nervous system that is characterized by varying symptoms. In some patients, seizures are sometimes

evoked by a specific stimulus. A seizure is a change in sensation awareness, or behaviour brought about by a brief electrical disturbance in the brain.

Seizures vary from momentary disruption of the senses, to short periods of unconsciousness or staring spells, to convulsions.The term "seizure" is widely used to describe an abnormal spasm or convulsions, generated by excessive electrical activity in the brain.[31]

Classifications of epileptic seizures

- **Generalized seizure (bilaterally symmetrical and without local onset**)
  - Tonic, clonic or tonic-clonic (Grandmal)
  - Absence (Petitmal)
    - Simple – Loss of consciousness only
    - Complex – With brief tonic clonic or automatic movements
    - Lennox – Gastautsyndrome
    - Juvenile myoclonic epilepsy
    - Infantile spasms (west syndrome)
    - Atonic (Astatic, akinetic) seizures (sometime with myoclonic jerks)
- Partial or focal seizures (Seizure beginning locally)
  - Simple (without loss of consciousness),
  - Motor (tonic, clonic, tonic-clonic, Jacksonian, benign childhood epilepsy, epilepsia partia continua)
  - Somatosensory or special sensory (visual, auditory, olfactory, gustatory,vertiginous).
  - Autonomic
  - Psychic
- Complex (with impaired consciousness)
  - Beginning as simple partial seizure and programming to impairment ofconsciousness.
  - With impairment of consciousness at onset.
- Special epileptic syndrome
  - Myoclonus and myoclonic seizure
  - Reflex epilepsy
  - Acquired aphasia with convulsive disorders

- Febrile and other seizure of infancy and childhood
- Hysterical seizures

This classification based mainly as the clinical form of the seizure and its electroencephalograph (EEG) features has been adopted worldwide is generally referred as to the international classification of epileptic seizures.[31]

Causes of Seizures

About 2% of adults have a seizure at some time during their life time. Most commonly, seizures disorders begin in early childhood or in late adulthood. Seizures starting before age 2 are usually caused by high fevers or metabolic disorders, such as abnormal blood levels of sugar (glucose), calcium, magnesium, vitamin B_6, or sodium. If the seizures reoccur, the cause is likely to be a hereditary brain disorder (such as nocturnal frontal lobe epilepsy)

Many seizures that begin between the ages of 2 and 14 years have no known cause. Seizures starting after age 25 may be caused by structural damage to the brain such as from a head injury, stroke or tumour. However, in about half of people in this age group, the cause is unknown. When no cause can be identified, seizures are called idiopathic.

People with a seizure disorder are more likely to have a seizure when they areunder excess physical or emotional stress or deprived of sleep.

Strong stimuli that irritate the brain-such as injury, certain drugs, sleep deprivation, infections, fever, low levels of oxygen in the blood, or very low levels of sugar in the blood can trigger a seizure whether a person has a seizure disorder or not. These seizures are known as "provoked seizures." Avoiding such stimuli can help prevent seizures. Rarely, seizures are triggered by repetitive sounds, flashing lights, video games,or even touching certain parts of the body. This disorder is called reflex epilepsy

Symptoms

Almost all seizures are relatively brief, lasting from a few seconds to a few minutes. Most seizures last 2 to 5 minutes. When a seizure stops, the person may

have a headache, sore muscles, unusual sensations, confusion, and profound fatigue. These after-effects are called the postictal state.

In some people, one side of the body is weak and the weakness lasts longer than the seizure (a condition called Todd's paralysis).

Symptoms vary depending on which area of the brain is affected by the abnormal electrical discharge. For example, if an abnormal electrical discharge occurs in the area that controls smell (located deep within temporal lobe), the person may sense an intensely pleasant or unpleasant smell. If it occurs in another area of the temporal lobe,the person may experience a sense of déjà vu, in which unfamiliar surroundings seem inexplicably familiar. If the abnormal discharge affects the frontal lobe, the person maybe unable to speak. If the abnormal discharge affects large areas, it can cause a convulsion (jerking and spasms of muscles, usually throughout the body). Other symptoms include numbness or tingling in a specific body part, brief attacks of altered consciousness (such as drowsiness), loss of consciousness, confusion, and loss of muscle or bladder control.

Symptoms also vary depending on whether the seizure is partial (affecting only one side of the brain) or generalized (affecting large areas on both sides of the brain).Partial seizures may be simple, in which a person is completely conscious and aware of the surroundings, or complex, in which consciousness is impaired but not completely lost. Partial seizures include simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua.

Generalized seizures cause a loss of consciousness and abnormal movements, usually immediately. Loss of consciousness may be brief or prolonged. Generalized seizures include tonic-clonic seizures, primary generalized epilepsy, absence seizures, atonic seizures, myoclonic seizures, and status epilepticus.

About 70% of people have only one type of seizure. The rest have two or more types.

For example, some children who have juvenile myoclonic epilepsy also have tonic-clonic seizures and absence seizures in addition to the myoclonic seizures, which usually involve the arms.

In simple partial seizures, electrical discharges begin in a small area and remain confined to that area.

Because only a small area of the brain is affected,symptoms are related to the function controlled by that area. For example, if the small area of the brain that controls the right arm's movements (in the left frontal lobe) is affected the right arm may begin to shake.

Jacksonian seizures produce symptoms that start in one part of the body, and then spread to another. Abnormal movements may occur in the hand or foot, then "march up"the limb as the electrical activity spreads in the brain. The person is completely aware of what is occurring during the seizure. Thus, Jacksonian seizures are simple partial seizures.

Complex partial (psychomotor) seizures usually begin with an aura that lasts 1 to 2 minutes. During the aura, the person starts to lose touch with the surroundings.During or immediately after the aura, some people stare, move the arms and legs in strange and purposeless ways, utter meaningless sounds, do not understand what other people are saying, and resist help. Other people are able to converse, but their conversation lacks spontaneity, and the content is some what sparse. This state may last for several minutes. People may then recover fully or the abnormal electrical discharge may spread to adjacent areas and to the other side of the brain. The result is a generalized seizure, which includes jerking of limbs, frothing at the mouth, and loss of consciousness.

An Epilepsia partialis continua is a rare type of continuous or frequently recurring partial seizure, usually affecting a hand or the face. Seizures occur every few seconds or minutes for days to years at a time. These seizures usually result from localized damage (such as scarring due to a stroke) in adults or from inflammation of the brain (such as encephalitis and measles) in children.

Tonic-clonic (grandmal) seizures usually begin with an abnormal electrical discharge in a small area of the brain, resulting in a complex partial seizure. However, the discharge quickly spreads to adjoining parts of the brain, causing the entire area to malfunction.

Primary generalized epilepsy begins with abnormal discharges in a large area of the brain. The abnormal discharges quickly spread to even more areas. In tonic clonic seizures and primary generalized epilepsy, abnormal discharges result in a temporary loss of consciousness and a convulsion, with severe muscle spasms and jerking throughout the body. The head may forcefully turn to one side, the teeth may clench, the tongue is often bitten, and bladder control may be lost. The seizures usually last 1to2 minutes. Afterward, the person may have a headache, be temporarily confused, and feel extremely tired. Usually, the person does not remember what happened during the seizure.

Absence (petitmal) seizures begin in childhood, usually between the ages of 5and 15. They do not produce the convulsions and other dramatic symptoms of tonicclonic seizures. A person does not fall down, collapse or move jerkily. Instead, the person has episodes of staring with fluttering eyelids and sometimes twitching facial muscles. The person is completely unaware of the surroundings. These episodes last 2 to3 seconds and, rarely, 10 to 30 seconds. The person abruptly stops activity and resumes it just as abruptly, experiencing no after-effects and not knowing that a seizure has occurred[32].

Atonic seizures which occur primarily in children, are characterized by complete loss of muscle tone and consciousness. They are brief, but they cause the child to collapse to the ground, increasing the risk of injury.

Myoclonic seizures are characterized by quick jerks of one or several limbs or the trunk. The seizures are brief and do not cause loss of consciousness, but they may occur repetitively[32].

In status epilepticus the most serious seizure disorder and a medical emergency,the seizure does not stop. Electrical discharges occur throughout the brain. The discharges produce a generalized seizure lasting more than 15 minutes or recurring seizures between which the person does not completely regain consciousness. The person has convulsions with intense muscle contractions and cannot breathe adequately. Without rapid treatment, the heart and brain can become over taxed and permanently damaged and the person may die. Seizures may have serious consequences[32].

Intense, rapid muscle contractions cancause injuries, including broken bones. Sudden loss of consciousness can cause serious injury due to falls and accidents. The turbulent electrical activity of convulsive seizures that reoccur without recovery between them can cause brain damage. Most people who have a seizure disorder experience dozens or more seizures in their lives without serious brain damage. A single seizure does not impair intelligence, but recurring convulsive seizures may eventually do so[32].

Diagnosis

People who have at least two unprovoked seizures that occur at different times have a seizure disorder. A diagnosis is made based on the person's history and the observations of eyewitnesses. Seizures may be suspected if symptoms such as loss of consciousness, muscle spasms that shake the body, loss of bladder control, sudden confusion, and an inability to pay attention occur. However, true seizures are much less common than most people think most episodes of brief unconsciousness are more likelyto be fainting.

An eyewitness report of the episode can be very helpful to doctors. An eyewitness can describe exactly what happened, whereas the person who had the episode usually cannot.

An accurate description of the circumstances is needed how fast the episode started whether it involved abnormal muscle movements (such as spasms of the head,neck, or facial muscles), tongue biting, or loss of bladder control how long it lasted and how quickly the person recovered. Doctors also need to know what the

person experienced before the episode whether the person had a premonition or warning that something unusual was about to happen and whether anything, such as certain sounds or flashing lights, seemed to trigger the episode.To help diagnosis a seizure disorder, doctors use electroencephalography (EEG), a painless safe proceedure that records electrical activity in the brain. Doctors examine the recording (electroencephalogram) for evidence of abnormal electrical discharges.

Because abnormal discharges are more likely to occur after too little sleep, EEG is sometimes scheduled after a person has been deprived of sleep for 18 to 24 hours. Even if a seizure did not occur during EEG, abnormalities may be present. Because of the limited recording time, EEG can miss abnormalities and the electroencephalogram may appear normal, even in people who have a seizure disorder.

Pathophysiology of Epilepsy[33]

An ideal account of the pathophysiology of epilepsy would provide an explanation for the clinical phenomenon of epilepsy in terms of events described at the cellular or molecular level. A great deal is known about abnormal patterns of electrical activity but can be recorded at the cellular level during octal or interracial activity, in both focal and generalized epilepsy. However, most of the clinical phenomena of epilepsy cannot yet be described in terms of molecular or cellular events.The action of physiological and pathological process in epileptic phenomena will be described under four headings.

- Systemic factors physiological and pathological that influence the occurrence of seizures.
- Epileptogenesis at the cellular level.
- Physiological events that occur as a result of seizures.
- Pathological changes that occur in the brain as a result of seizure.

The apparently clear, logical distinction between cerebral pathology, which is a direct or indirect consequences of fits cerebral pathology which is cause of fits and pathology which occurs coincidentally in the brains of epileptic patients is not easily made in practice.

The difficulty in distinguishing group is that pathology arising as a direct consequence of seizures is of an anoxic-ischemic kind and may therefore being distinguishable from pathology arising from, say, perinatal asphyxia or later cardiac or cerebrovascular disorders. This problem is most severe from chronic lesions in the brains of patients who have had epilepsy for the greater part of their lives. It is less severe inpatients die within a few hours or days after an episode of status epilepticus and showing only acute lesions in the brain.

The major neurotransmitters involved in epileptic seizures are[33]

- Gamma amino butyric acid (GABA)
- Acetylecholine
- Glycine
- Glutamate and aspartate
- Catecholamines

Drug therapy of epilepsies[33]

Theoretically anticonvulsant might act directly on the epileptogenic focus or to prevent the generalization of seizure activity throughout the brain since they may prevent convulsions but do not alter the interracial EEG-record.

The treatment of patients with convulsive seizures can be considered in four parts.

- Identification and elimination of factors that might cause or precipitate attacks.
- Drug therapy to prevent attack.
- Sustaining mental and physical health aid.
- Surgical therapy in selected patients with seizures of focal origin.

The basic approach to anticonvulsant therapy is to select an appropriate drug for the specific type of seizure disorder and to progressively increase the dose.Until seizures are controlled or toxic side effects limit further increments.

Treatment of specific seizure type

If the cause can be identified and eliminated, no additional treatment is necessary.For example, if low sugar (glucose) levels in the blood (hypoglycaemia) caused the seizure, glucose is given to increase the levels and the disorder causing

the low levels is treated. Other treatable causes include a tumour, an infection and abnormal sodium levels.

Anticonvulsants may be needed to reduce the risk of having another seizure. Anticonvulsants are not usually prescribed for people who have had only one generalized seizure for which no cause can be found. But they are necessary for people who have had more than one, unless the cause has been identified and completely eliminated.

Anticonvulsants can completely prevent convulsive seizures in more than half the people .These drugs are only slightly less effective for absence seizures. Half of the people who respond to anticonvulsants can eventually discontinue them without having a relapse.

Mechanism of action of anticonvulsant drugs[33]

There are two general ways in which drugs might abolish or attenuate seizures through effects on pathologically altered persons of seizure foci to prevent or reduce their excessive discharge, and through effects that would reduce the spread of excitation from seizure foci and prevent detonation and disruption of function of normal aggregate of neurons.

Pharmacological modification of GABA or glutamate medicated transmission hasa strong effect on the epileptic discharge.

Facilitation of GABA-mediated inhibition could in principle be achieved in various ways. Many of the clinically effective anticonvulsant (e.g. phenobarbitone and benzodiazepines) enhance the inhibitory effect of GABA by facilitating the GABA mediated opening of chloride channels.

Phenytoin has also been reported to affect other aspects of membrane function, including inhibition of calcium entry, and post-tetanic potentiation as well as intracellular protein phosphorylation by calmodulin activated kinase, which could also interface with membrane excitability as well as synaptic mechanism.

Table No.3: List of Classification of anticonvulsant drugs

S.NO	Type	Drugs	Seizure type
1.	Barbiturates	Phenobarbital,Primidone	Simple partial, Complex partial, Generalized tonic clonic seizures
2.	Hydantoins	Phenytoin,Mephenytoin	Simple partial, Complex partial, Generalized tonic clonic seizures
3.	Benzodiazepines	Diazepam, Clonazepam,Lorazepam	Simple partial, Complex partial, Absence seizures
4.	Oxazolidinediones	Trimethadione,Paramethadione	Simple partial, complex partial, Absence seizures
5.	Succinimides	Ethosuccimide, Methosuccimide	Absence seizure
6.	Valproic acid derivatives	Valproic acid, Divalproex sodium	Myoclonic, Tonic clonic seizures
7.	Tricyclics	Carbamazepine	Simple partial, Complex partial, Generalized tonic clonic seizures Myoclonic, Tonicclonic

DIARRHOEA

Diarrhoea is a very common problem in the tropical and subtropical countries, it can be caused by variety of condition varying from infection and allergy to emotional disturbances. It is defined as the frequent passage of liquid faeces with or without blood or mucous[34]. Diarrhoea is a disease constituted a major cause of morbidity and mortality worldwide, specially in developing countries. More than 5 million children under the age of 5 years die to diarrhoea every year. A nationwide study has estimated that diarrhoea kills > 1 million children in India annually. Recurrent or protracted diarrhoea is also a major cause of protein-calorie malnutrition in developing countries. Even mild diarrhoea and that in adults, is a disabling symptom and an inconvenience[35].

Relevant pathophysiology[35]

Water and electrolytes are absorbed as well as secreted in the intestine. Jejunum is freely permeable to salt and water which are passively absorbed secondary to nutrient (glucose, amino-acids etc.) absorption. In the ileum and colon active Na^+K^+ATPase medicated such absorption occurs, primarily in the mature cells lining the villous tips, water follows isosmotically. In addition glucose facilitated Na^+absorption takes place in the ileum one Na^+ion is transported along with each molecule of glucose. This mechanism remains intact even in severe diarrhoeas.The osmotic load of luminal contents plays an important role in determining final stool water volume.

When non-absorbable solutes are present and in disaccharide deficiency (which occurs during starvation), the stool water is increased. Inhibition of Na^+K^+ATPase and structure damage to mucosal cell (by Rota virus) causes diarrhoea by reducing absorption.

Intercellular cyclic nucleotides are important regulators of absorptive and secretory processes. Stimuli enhancing cAMP or cGMP cause net loss of salt and water both by inhibiting Na^+Cl^- absorption in villous cells and by promoting anion secretion (Na^+ accompanies) in the crypt cells which are primarily secretory.

Many bacterial toxins, e.g., cholera toxin, exotoxin elaborated by *Enterotoxigenic Escherchia. coli* (ETEC), *Staphyllococcus aureus, Salmonella* etc. activate adenylyl cyclase which enhances secretion that reaches its peak after 3-4 hours and persists until the stimulated cells are shed in the normal turnover i.e. 36 hours after a single exposure. Concurrent inhibition of absorption adds to the rate of salt and water loss. Prostaglandins (PGs) and intracellular Ca^{2+} also stimulated the secretary process. All acute enteric infections produce secretary diarrhoea. The heat stable toxin (ST) of ETEC, *Clostridium difficile* and *Entamoeba histolytica* cause accumulation of cGMP which also stimulates anion secretion (less potent than cAMP) and inhibits Na^{+} absorption.

Diarrhoea associated with carcinoid (secreting 5-HT) and medullary carcinoma of thyroid (Secreting calcitonin) is mediated by cAMP. Excess of bile acids also cause diarrhoea by activating adenylyl cyclase.

Principles of Management[35]

Rational management of diarrhoea depends on establishing the underlying cause and instituting specific therapy, only if necessary, since most diarrhoeas are self-limiting. Majority of enteropathogens are taken care of by motility and other defense mechanism of the gut.

Therapeutic measures may be grouped into

(a) Treatment of fluid depletion, shock and acidosis.

(b) Maintenance of nutrition

(c) Drug therapy.

The relative importance of each is governed by the severity and nature of diarrhoea.

Rehydration[35]

In majority of cases, this is the only measure needed. Rehydration can be done orally or i.v.

Intravenous rehydration[35]

It is needed only when fluid loss is sever i.e., >10%body weight, or if patient is losing 10 ml/kg/hr, or is unable to take enough oral fluids due of weakness, stupor or vomiting. This provides 133 mM Na^+, 13 mM K^+, 98 mMCl^- and 48 mM HCO_3^-. Ringer lactate (Na^+ 130, Cl^- 109, K^+ 4, lactate 28 mM) recommended by WHO (1991) could be used alternatively.Volume equivalent to 10% body weight should be infused over 2-4 hours,the subsequent rate of infusion is matched with the rate of fluid loss. In most of cases, oral rehydration can be instituted after the initial volume replacement.

Oral rehydration[35]

Advent of oral rehydration therapy (ORT) is considered a major advance of recent times. If the fluid loss is mild (5-7% body weight) or moderate (7.5-10%body weight) ORT can be instituted from the very beginning.

Rationale of ORS composition[35]

Oral rehydration is possible if glucose is added with salt. It capitalises on the intactness of glucose facilitated Na^+ absorption, even when other mechanisms have failed or when or when intestinal secretion is excessive,the secreted fluid lacks glucose and cannot be reabsorbed. The composition of oral rehydration salt/solution (ORS) has been debated.

The general principles are[35]

- It should be isotonic (diarrhoea fluids are approximately isotonic with plasma). The molar ratio of glucose should be some what higher than Na^+ (excess glucose will be utilized, in absorbing Na^+ present in the intestinal secretion in addition to present in ORS itself)

- Enough K^+ and HCO^-_3 should be provided to make up the losses in stool.

The WHO has recommended a universal formula

NaCl 60mM = 3.5gm,
KCl20mM = 1.5gm
Sod.Citrate 30mM = 2.9gm
Glucose 110mM = 20gm

} to be dissolved in 1 L of water

This provides Na^+ 90mM, K^+ 20mM, Cl 80mM, citrate (base) 30mM and glucose 110mM. It has been argued that the composition of ORS should be varied according to that of the diarrhoea stool.

Administration of ORT patients are encouraged to drink ORS at ½ -1 hourly intervals, initially 5-7.5% body weight volume equivalent is given in 2-4 hours. Thirst due to volume depletion provides an adequate driving force. Subsequently it may be left demand, but should at least cover the rate of loss in stools. In a week child who refuses to drink the ORS at the desired rate it can be given by intragastric drip restoring hydration in 6 hours should be aimed.

ORT is not designed to stop diarrhoea, but to restore and maintain hydration, electrolyte and pH balance until diarrhoea ceases, mostly spontaneously. It is the best and not a second choice approach to i.v.hydration.About 300 million liter of ORS is being used annually, and is estimated to be preventing 0.5 million child deaths world wide.

Maintenance of nutrition[35]

Country to traditional view, patients of diarrhoea should not be starved. Fasting decreases brush border disaccharide enzymes and reduces absorption of salt, water and nutrients may lead malnutrition if diarrhoea is prolonged or recurrent. Feeding during diarrhoea has been shown to increase intestinal digestive enzymes and cell proliferation in mucosa, simple foods like breast milk or half strength buffalo milk, boiled potato, rice, chicken soup, banana, sago etc. should be given as soon as the patients can eat.

Drug Therapy[35]

It consists of

1. Specific antimicrobial drug
2. Nonspecific antidiarrhoeal drug.

Antimicrobials

One or more antimicrobial agent is almost routinely prescribed to every patient of diarrhoea. In fact such dug have a limited role in the overall treatment of diarrhoeal patients the reasons are

- Bacterial pathogen is responsible for only a fraction of cases.
- Even the bacterial diarrhoea, antimicrobials alter the course of illness only in selected cases.
- Antimicrobials may prolong the carrier state

Diarrhoea patients can generally be placed in one of the two categories.abundant watery diarrhoea lacking mucus or blood, usually dehydrating with frequent vomiting but little or no fever. They are generally caused by adhesive but non-invasive enterotoxigenic bacteria such as Cholera, ETEC, *Salmonella enteritids* or by rota and other virus which stimulate massive secretion by activating cAMP, ORS and not antimicrobials are the main therapy.

- Slightly loose smaller volume stools, frequently with mucus and/or blood, mild dehydration, usually attended with fever and abdominal pain but not vomiting are generally by enteroinvasive organisms like *shigella* enteropathogenic *Escherchia, coli* (EPEC)

Antimicrobial are of no value[35]

In diarrhoea due to non-infective causes, such as

- Irritable bowel syndrome
- Coeliac disease
- Pancreatic enzyme deficiency
- Tropical spare (except when there is secondary infection)
- Thyrotoxicosis

Rotavirus is an important pathogen of acute diarrhoea, specially in children in developing countries.

It along with other diarrhoea causing virus, is not amenable to chemotherapy.

Salmonella food poisoning is generally a self-limiting diseases. Antibiotic have been widely used, but may be harmful rather than beneficial – treated patients pass organisms in stool for longer periods than untreated patients.

Antimicrobial useful only severe disease (but not in mild cases)[35]

- Travellers diarrhoea mostly due to ETEC, *Campylobacter* or virus cotrimoxazole, norfloxacin, doxycycline and erythromycin shorten theduration and total fluid needed only in severe cases.
- ETEC It is less common, but causes *Shigella* like invasive illness. Cotrimoxazole, colistin, nalidixic acid or norfloxacin, may be used in acute cases and in infants.
- *Shigella* enteritis Only when associated with blood and mucus in stools maybe treated with ciprofloxacin, norfloxacin or nalidixicacid. Cotrimoxazole and ampicillin are alternatives, but may strains are resistant to these.
- *Salmonella typhimurium* enteritis It is often invasive severe cases may betreated with a fluoroquinolone, Cotrimoxazole or ampicillin.
- *Yersinia enterocolitica* Common in colder places, not in tropics. Cotrimoxazole is the most suitable drug in severe cases; ciprofloxacin is an alternative.

Antimicrobials regularly used in[35]

- Cholera though not life saving, tetracyclines reduce the stool volume to nearly half.cotrimoxazole is an alternative, specially in children. Recently multiple drug resistant cholera strains have arised. Diarrhoea can be treated with ciprofloxacin / norfloxacin. furazolidone and erythromycin
- For infections caused by *Campylobacter jejuni* Norfloxacin and other furazolidone eradicate the organism from the stools and control diarrhoea. Erythromycin and furazolidone are fairly effective.
- Diarrhoea associated with bacterial growth in blind loops/diverticulitis may be treated with tetracycline or metronidazole.
- For Amoebiasis metronidazole, diloxanide furoate, Furazolidone are effective drugs.

Drugs controller of India has banned the following category of antidiarrhoeal drugs[35]

- Containing adsorbent like kaolin, pectin, attapulgite, activated charcoal etc.,
- Containing phthalylsulfathiazole, succinylsulfathiazole, sulfaguanidine, neomycin, streptomycin, dihydrostreptomycin.
- For pediatric use containing diphenoxylate, loperamide, atropine, belladonna, hyosciamine, halogenated hydroxyquinolines,
- Fixed dose combinations of anti-diarrhoeals with electrolytes

Drug which causes diarrhoea[35]

Antibiotics-	Clindamcin, Tetracyclines and Sulfonamides.
Antihypertensive-	Reserpine, Methlydopa and Guanethidine.
Cholinergics-	Bethanechol, Metochlorpropamide and Neostigmine.
Cardiac agents-	Digitalis, Digoxin and Quinidine.

Literature survey showed the following plant's have protective effect on diarrhoea

a) Rhizomes of *Nelumbo nucifera*[36]
b) Stem bark of *Zanthoxylum rhesta*[37]
c) Seeds of *Holarrhena antidysenterica*[38]
d) Roots of *Hemidesmus indicus*[39]
e) Roots of *Asparagus pubescens*[40]
f) Seeds of *Abrus precatorius*[41]
g) Barrk of *Egletes viscosa*[42]
h) Leaf of *Psidium guajava*[43]
i) Stem bark of *Dalbergia lanceolaria*[44]
j) Seed of *Punica granatum*[45]

2. LITERATURE REVIEW

- **M.N.Vinay Suvarna[46] *et al.*, 2013** evaluated the antioxidant activity of *Artocarpus hirsutus* methanolic fruit extract: In an *in vitro* study results were shown that methanolic fruit extract of *Artocarpus hirsutus* was found to be effective in DPPH radical scavenging activity. The DPPH radical scavenging effect of extract was increased with increased concentration of methanolic plant extract

- **A.K. Azeem[47] *et al.*, 2013** investigated the fruits of the plants *Artocarpus hirsutus* Lam. and were used to evaluate the diuretic activity by modified Lipchitz method.. The parameters studied were volume of urine, concentration of excreted ions of sodium and potassium, ratio of sodium ions to potassium ions excreted etc. Furosemide was used as the reference standard. Though both the extracts shown significant diuretic activity on the various parameters tested, the aqueous fruit extract was found to be having potent diuretic property

- **Lakshmi Pethamkamsetty[48] *et al.*, 2013** performed the Phytochemical and biological examination of the root extract of *Artocarpus hirsutus* Lam. showed the presence of isoprenylated flavonoids and the work was further extended to test the crude extracts for antibacterial and antifungal activities. The results from the present study have shown that have considerable activity against selected bacterial and fungal strains which can be attributed to the presence of steroidal and phenolic compounds in the crude extracts of *Artocarpus hirsutus* Lam.

- **Eke Ifenayi Gabreiel[49] *et al.*, 2013** evaluated the antiulcer properties of the aqueous methanolic leaf extract of *Palisota hirsuta* (MLEPH) against experimentally induced gastric ulceration in mice. The results indicated that the MLEPH at all doses significantly reduced ($P<0.05$), the mean ulcer index was significantly reduced by 50 and 100 mg/kg in aspirin induced ulcer model as compared to control. In ethanol induced gastric ulceration model, MLEPH at 50 mg/kg reduced the ulcer preventive index significantly ($P>0.05$)

- **Om Prakash[50] *et al.*, 2013** evaluated the anticonvulsant activity of *Artocarpus heterophyllus* Lam. Leaves (Jackfruit) in mice by maximum electroshock (MES) and strychnine induced convulsions models in swiss albino mice. The results were shown that methanolicplant extract exhibited a dose dependent significant ($P<0.01$) reduction in various phases of epileptic seizures on comparision with reference standard diazepam 5 mg/kg, p.o

- **Gulab S. Shinde[51] *et al.*, 2013** evaluated the anticonvulsant activity of *Careya arborea* Linn. bark against experimental induced seizures. Convulsions were induced by maximum electroshock seizures(MES) using standard phenytoin 25 mg/kg i.p.The results indicated that the methanolic and aqueous extract of *Careya arborea* Linn. bark at 300 mg/kg b.wp.o showed the most significant ($P<0.01$) anticonvulsant effect by decreasing the duration of hind limb extension (extensor phase) and also duration of as compared with control in maximum electroshock induced seizures

- **Ndukui James Gakunga[52] *et al.*, 2013** evaluated the antidiarrheal activity and phytochemical profile of the ethanolic leaf extract of *Leonotis nepetifolia* (Lion's ear) in wistar albino rats by castor oil induced diarrhea. The extract of *Leonotis nepetifolia* inhibited castor oil induced diarrhea in wistar albino rats at doses of 225, 400 and 900 mg/kg. Castor oil was used to induce diarrhea and wet faecal counts were determined at hourly intervals. The results indicated that the extract significantly reduced the number of wet faecal pellets with extract treated groups showing lower diarrhoeal activity than the negative control

- **Amitabha Dey[53] *et al.*, 2013** evaluated the antidiarrhoeal activity of ethanolic leaf extract of *Scoparia dulcis* Linn. on wistar albino rats. The extract was evaluated for castor oil induced diahorrea and intestinal transit in rats by charcoal meal. The results shown that the extract of *Scoparia dulcis* Linn. was similar to that of standard drug loperamide (3 mg/kg) which prouduced an inhibition of 70.38% significantly ($P<0.05$) reduces frequency of stooling in castor oil induced diahorrea and intestinal motility in rats

- **Jigna S. Shah, Jetun R Patel[54] *et al.*, 2012** evaluated the mechanism of action of herbal formulation Lucer against experimentally induced gastric ulcers. The results indicated that the aqueous extract (120 and 180 mg/kg) of Lucer was found to be very effective in gastric ulceration and ulcer index parameters

- **Amol N. Patil[55] *et al.*, 2012** performed the antiulcer effect of amlodipine and compared it with ranitidine by indomethacin, alcohol and pylorus ligation–induced gastric ulcer model in rats. The results indicated that the significant decrease in ulcer index and gastric pH as compared to control. Amlodipine prouduced significant antiulcer effects in all experimental models

- **D. Champatisingh[56] *et al.*, 2011** evaluated the anticataleptic and antiepileptic activity of ethanolic extract of leaves of *Mucuna pruriens*. A study on role of dopaminergic system in epilepsy in albino rats. The results were shown that *Mucuna pruriens* had significant anticataleptic and antiepileptic activity in HIC, MES,PISE(PISE)

- **R.Sathish[57] *et al.*, 2011** evaluated the ethanolic extract of *Passiflora foeida*(EEPF) whole plant on gastric ulcer.The antiulcer effects of EEPF at 100 mg/kg and 200 mg/kg doses were evaluated on ethanol and aspirin-induced gastric ulcer models. The results indicated that the histological changes in gastric tissue of ulcer rats were determined in both the models and ethanolic extract of *Passiflora foetida* treatment significantly ($P<0.01$) reduces the ulcer index of both ethanol and aspirin-induced ulcer rat model

- **Saranya Paneer Selvam[58] *et al.*, 2011** evaluated the gastroprotective effect of hydroalcoholic extract of *Andrographis paniculata* (HAEAP) in male wistar albino rats. Rats pretreated with HAEAP (100,200,500 mg/kg b.wt for 30 days) and gastric ulcers induced by ethanol, aspirin, pylorus ligation and cold restraint ulcer models. The results indicated the ulcer score was found to be low in HAEAP-pretreated rats. Among the doses studied, 200 mg/kg body weight was found to be optimum for significant ulcer reduction

- **Pandian Nagakannan[59] *et al.*, 2011** evaluated the sedative and antiepileptic activities of ethanolic extract of *Anthocephalus cadamba* Roxb. in mice and rats. The results were shown that ethanolic extract of *Anthocephalus cadamba* Roxb significant increase in ketamine induced sleeping time. It also exhibited significant increase ($P<0.05,0.01$ and 0.001) in latency to clonic convulsion and tonic extension

- **Pooja Sinoriya[60] *et al.*, 2011** investigated the anticonvulsant and muscle relaxant activity of the ethanolic extract of stems of *Dendrophthoe* (Linn.F) in mice. The results were shown that ethanolic extract of *Dendrophthoe* (Linn.F) at a dose of (100,300 and 500mg/kg, p.o) significantly ($P<0.01$) inhibited seizures induced by MES, reduced the duration of hind limb tonic extensor phase (HLTE) and decline in motor coordination

- **Dibinlal D[61] *et al.*, 2010** studied the pharmacognostical studies on the bark of the *Artocarpus hirsutus* Lam. *Artocarpus hirsutus* Lam., (Wild jack) belonging to the family Moraceae a large evergreen tree up to 70m height, found up to an altitude of 1200m in evergreen india. The wood is straight blackish brown in color

- **G. Vinothapooshan[62] *et al.*, 2010** evaluated the antiulcer activity of *Mimosa pudica* leaves against gastric ulcer in rats. The effect of methanolic, chloroform and diethyl ether extracts of *Mimosa pudica* was investigated in rats to evaluate the antiulcer activity by using three models, i.e. aspirin, alcohol and pyloric ligation models experimentally induced gastric ulcer. The results indicated that the alcoholic extract significantly ($P<0.001$) decreased the volume of gastric secretion, pH and ulcer index with respect to control

- **Vivek Sharma[63] *et al.*, 2010** evaluated the ethanolic and aqueous extracts of aerial parts of *Caesalpinia pulcherriima* Linn. for anti-inflammatory and antiulcer activities. The results were shown that ethanolic and aqueous extracts of *Caesalpinia pulcherriima* Linn. significantly decreased ($P<0.01$) the granuloma tissue development. Both ethanolic and aqueous extract of *Caesalpinia pulcherriima* exhibited significant ($P<0.01$) antiulcer activity by decreasing the ulcer score in both the ulcer models

- **A. Vijayalakshmi[64] *et al.*, 2010** evaluated the anticonvulsant activity and neurotoxicity of ethanolic extract and ethyl acetate fraction of the rhizome of *Smilax china* Linn(EESC and EAF) in mice. The results were shown that duration of hindleg extension in MES test was significantly (P<0.001) reduced by EESC at a dose level of 400 mg/kg and EAF at both higher dose levels (200 mg/kg and 400 mg/kg)

- **P. Paneerselvam[65] *et al.*, 2010** evaluated anticonvulsant activity Schiff bases of 3-Amino-6, 8-dibromo-2-phenyl-quinazolin-4(3H)-ones on albino mice by maximal electroshock method using phenytoin as a standard.The compound bearing a cinnamyl function displays a very high activity (82.74%) at dose level of 100 mg/kg b.w

- **Supawatchara Singhatong[66] *et al.*, 2010** evaluated the antioxidant and toxicity activities on heartwood extract of *Artocarpus lakoocha* Roxb. The results were shown that the antioxidant activity of *Artocarpus lakoocha* Roxb was due to presence of flavonoid, phenolic acids or phenolic di-termenes which attributes to its potent antioxidant activity

- **Khushtar[67] *et al.*, 2009** investigated the protective effect of ginger oil on aspirin and pylorus ligation-induced gastric ulcer model in rats. In wistar albino rats which ability of ginger oil to provide gastric protection was studied at two different doses, 0.5 and1gm/kg p.o. Gastric protection was evaluated by measuring the ulcer index, serum *y*-GTP levels, total acidity of gastric juice and gastric wall mucus thickness. The results obtained in present study indicated that ginger oil has a protective action against gastric ulcers induced by aspirin pylorus ligation in wistar albino rats

- **P. Thirunavakkarasu[68] *et al.*, 2009** evaluated the antiulcer activity of ethanolic extract of *Excoecaria agallocha* bark on NSAID-induced gastric ulcer in albino rats. The results were showed that was elevated in the gastric juice of untreated rats and hear normal levels in pretreated rats. The ethanolic extract of *Excoecaria agallocha* bark was able to decrease the acidity and increase the mucosal defense in the gastric areas, there by justifying its use an antiulcerogenic agent

- **Karunakar Hegde[69] *et al*., 2009** evaluated the anticonvulsant activity of ethanolic extract of roots of *Carissa caranda* Linn, on electrically and chemically induced seizures. The results were shown at a dose of (100-400 mg/kg) significantly reduced the duration of seizures induced by maximal electroshock (MES). However, only 200 mg/kg and 400mg/kg of the extract conferred protection (25 and 50%, respectively) on the mice

- **Danjuma N.M[70] *et al*., 2009** evaluted the anticonvulsant activity of hydroalcoholic stem bark extract of *Randia nilotica* Stapf. In mice and chicks. The results were shown that the test systems selected were maximal electroshock test in chicks, pentylenetetrazole (PTZ) induced seizure and strychnine (STN) induced seizure tests in mice. The mean number of myoclonic body twitches was significantly ($P<0.05$) reduced by the extract in the PTZ test as 5 mg/kg body weight showed a 27 % decrease while 10 and 20 mg/kg showed 59 % and 61 % reduction respectively. Phenobarbitone (30 mg/kg) used as control showed a 95 % decrease. The results obtained indicated potential anticonvulsant activity of the stem bark extract of *Randia nilotica* Stapf

- **P. Malairajan[71] *et al*., 2008** evaluated the antiulcer activity of ethanolic extract of *Polyalthia longifolia* Sonn. in experimental animals. The results indicated that a significant ($P<0.01$,$P<0.001$) antiulcer activity was observed in all the models. It also showed 89.71% ulcer inhibition in ethanol induced ulcer and 95.3% ulcer protection index in stress induced ulcer

- **Salaj Khare[72] *et al*., 2008** evaluated antiulcer effect of cod liver oil(0.5 gm/kg, p.o and 1 gm/kg, p.o.) on gastric and duodenal ulcer in rats .The results were shown that both doses of cod liver oil showed gastric ulcer healing effect in acetic acid induced chronic gastric ulcer, prouduced gastric antisecretory effect in pylorus ligated rats and also showed gastric cytoprotective effect in ethanol induced and indomethacin induced ulcer. The highest dose of cod liver oil (1 gm/kg, p.o.) was more effective compared to the low dose (0.5 gm/kg, p.o.).

3. OBJECTIVE OF THE WORK

Gastrointestinal disorders are one of the severe classes of human ailments causing maximum discomfort, morbidity and mortality. Peptic ulcer is a benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to acid and pepsin. There are several causes including, stress, alcohol consumption, cigarette smoking, H. pylori infection, ingestion of drugs and chemicals. Especially consumption of alcohol for a prolonged period, smoking of cigarettes, or chronic consumption of NSAIDs are causing peptic ulcers[12].

Epilepsy is a group of chronic neurological disorders characterized by sporadiac episodes of convulsive seizures, sensory disturbance, abnormal behaviour, and loss of consciousness or all of these symptoms resulting from a brain dysfunction or anabnormal discharge of cerebral neurons[29,30]. In some patients, seizures are sometimes evoked by a specific stimulus. A seizure is a change in sensation awareness, or behaviour brought about by a brief electrical disturbance in the brain. Seizures vary from momentary disruption of the senses, to short periods of unconsciousness or staring spells, to convulsions. The term “seizure” is widely used to describe an abnormal spasm or convulsions, generated by excessive electrical activity in the brain[31].

Diarrhoea is very common problem in the tropical and subtropical countries, it can be caused by variety of condition varying from infection and allergy to emotional disturbances. It is defined as the frequent passage of liquid faeces with or without blood or mucous[34]. Diarrhoea disease constituted a major cause of morbidity and mortality worldwide specially in developing countries. More than 5 million children under the age of 5 years die to diarrhoea every year. A nationwide study has estimated that diarrhoea kills > 1 million children in India annually. Recurrent or protracted diarrhoea is also a major cause of protein-calorie malnutrition in developing countries. Even mild diarrhoea and that in adults is a disabling symptom and an inconvenience[35].

Thus the objective of the present study is to evaluate the Antiulcer, Anticonvulsant and Antidiarrhoeal activities of *Artocarpus hirsutus* Lam.

Based on the Literature review, it was planned to carry out the work as outlined below:

I) Extraction

II) Preliminary Phytochemical screening

III) Analytical determination

HPTLC analysis

IV) Toxicity studies

Acute oral toxicity: Guideline number - 423

V) Pharmacological evaluation

A. Antiulcer activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* (**MELAH**)

i) Ethanol induced ulcer

ii) Aspirin induced ulcer

B. Anticonvulsant activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* **(MELAH)**

i) MES induced convulsions

C. Antidiarrhoeal activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* (**MELAH**)

i) Castor oil induced diarrhoea

4. PLANT DESCRIPTION

AUTHENTICATION CERTIFICATE

Dr. V. NANDA GOPALAN, M.Sc., M.Phil., Ph.D,
Associate Professor

NATIONAL COLLEGE, (AUTONOMOUS)
(Nationally Accredited at 'A' Level by NAAC)
Department of Botany
Tiruchirapalli - 620 001.
Tamil Nadu, India.

Email : tvn135@yahoo.co.in

PLANT AUTHENTIFICATION CERTIFICATE

This is certify that plant given by **Mr. J. SARAVANA KUMAR** M.Pharm student of **DR. S. KARPAGAM KUMARA SUNDARI** M.Pharm., Ph.D., Authentically identified as ***Artocarpus hirsutus Lam.*** *belongs* to family **Moraceae.**

Dr. V. NANDAGOPALAN, M.Sc., M.Phil., Ph.D.,
Associate Professor
Department of Botany
National College (Autonomous)
Tiruchirapalli - 620 001
Tamil Nadu, India.

COLLECTION OF PLANT SPECIES

The leaves of *Artocarpu shirsutus Lam.*are collected from the Western Ghats of kerela.

Fig. 1: Leaves of *Artocarpushirsutus*Lam .

Fig.2: Tree of *Artocarpus hirsutus*Lam.

PROFILE OF THE SELECTED SPECIES

***Artocarpus hirsutus* Lam.**

SYNONYMS

Artocarpushirsuta Lam.Aini , Aini-maram, Aani, Anhili and Anjili[78,79,80]

VERNACULAR NAMES

English	:	Wild jack , Hirsute Artocarpus
Tamil	:	Aiyinipila ,Anjili
Kannada	:	Hebbalasu
Malayalam	:	Ayani, Anjili, Anniliayar
Others	:	KaduHalasu[78,79,80]

TAXONOMICAL CLASSIFICATION

Kingdom	**:**	Plantae
Phylum	**:**	Magnoliopsida
Class	**:**	Magnoliopsida
Order	**:**	Rosales
Family	**:**	Moraceae L.
Genus	**:**	*Artocarpus* L.
Species	**:**	*hirsutus*L.

DESCRIPTION AND HABITAT

The plant *Artocarpus hirsutus* Lam. (Moraceae) is a large evergreen tree up to 70m in height, found up to an altitude of 1200m in evergreen forest of peninsular India. The outer colour of bark is grey and inner color is brown. Leaves are simple and dark green and rhomboid or ovate and dark green in color[46,47].

Leaves are simple, alternate, spiral, clustered at twigs end, stipules to 2.5 cm long, lanceolate, tawny hirsute,caducous, leaving annular scar petiole 1.3-3 cm long, stout, subterete or planoconvex, hirsute lamina 10-30.5 x 5-14 cm, usually ovate to broadly elliptic, apex subacute or shortly acuminate, base rounded or subacute, margin

entire or undulate (lobed when young), coriaceous, drying brown, densely hirsute beneath when young, later become glabrous except on midrib and nerves, midrib flat above secondary nerves 10-12 pairs, ascending and tertiary nerves broadly reticulo-percurrent. The branchlets are covered with rust-brown hairs. Inflorescence is axillary. The female inflorescence is globose with individual flowers embedded in its axis. Male flowers consisting of a single stamen are inconspicuous and are borne on an elongate inflorescence[81,82]. The female inflorescence with itsconstitutent flowers forms a multiple fruit similar to Jack fruit but is not as big the fleshy and juicy sepals and petals being the edible part.The timber of this tree is hard and durable .Evergreen trees, to 50 m high, bark 10-15 mm thick, surface dull grey-brown, smooth, lenticellate, exfoliations thin, exfoliated surface red, fibrous blaze creamy turning to pinkish-yellow exudation milky white, sticky, branchlets hirsute. Leaves simple, alternate; stipules to 4 cm long, lateral, densely tawny strigose petiole 10-30 mm long, stout, hirsute; lamina 13-25 x 7.5-15 cm, broadly ovate, obovate or elliptic, base acute, obtuse or round, apex subacute or very shortly acuminate, margin entire, undulate, coriaceous, glabrous above, hirsute-pubescent beneath lateral nerves 6-12 pairs, pinnate, prominent intercostae scalariform, faint. Flowers unisexual, minute, yellowish-green male in axillary, pendulous, narrowly cylindric spikes upto 15 cm long tepals 2, united below stamen 1 anther exserted, ovate, bracteoles chaffy female flowers in axillary ovoid spikesperianth tubular, confluent below with the receptacle ovary superior, straight, ovule pendulous style exserted stigma undivided[46,47].

Fruit a sorosis 6-7.5 cm across, globose or ovoid, echinate, yellow when ripe, the spines cylindrical, straight, hispid, perforate at the apex for filiform style seeds 16-18 mm long, ovoid, white[78,79,80].

THERAPEUTIC USES

Anti microbial, anorexia and treatment for burning sensation. The main property and uses of unripe fruits are sour, astringent, sweet and thermogenic. An aphrodisiac, constipating and cause flatulence[83,84].

5. MATERIALS AND METHODS

Plant Extraction[46,50]

The leaves of *Artocarpus hirsutus* Lam. were collected from Punalur, Kollam district, Kerala, India. Care was taken to collect only the healthy leaves. The collected leaves were authenticated at the Department of Botany, National College, Tiruchirapalli, Tamilnadu, India. The leaves were then shade dried, coarsely powdered in such a way that it passed through sieve no. 20 and was retained on sieve no. 40. About 500gm of the dry powder was extracted continuously in soxhlet apparatus with 99% methanol for 72 hrs. After 72hrs, the solvent was evaporated to obtain the crude extract. The extract was then dried under vaccum and suspended in water before use.

Fig.3: Soxhlet apparatus

Analytical determination

HPTLC analysis[73,74]HPTLC analysis was carried out following Harborne and Wagner *et al*. For the present study CAMAG HPTLC system equipped with LinomatV applicator, TLC scanner 3 and reprostar 3 controlled by WinCATS-4 software were used. A total of 102 mg extract was dissolved in 10 ml of methanol (95%) and the solution was centrifuged at 3000 rpm for 5 min and used for HPTLC analysis as test solution. The samples (5and 10µl) were spotted with a 100 µl Hamilton syringe on a pre-coated silica gel glass plate 60 F_{254} (20 x 10 cm) (E.Merck) of uniform thickness 0.2mm with aluminium sheet support using a CamagLinomat V. The plates were pre-washed by ethanol and activated at 60^{o}C for 5 min pror to chromatography. The sample loaded plate was kept in Camag TLC glass twin trough developing chamber (after saturated with solvent vapour) with respective mobile phase and the plate was developed up to 90mm in the respective mobile phase. The Toluene: Ethyl Acetate: Formic acid (5:4:1) was employed as mobile phase. Linear ascending development was carried out in 20 cm x 10cm twin trough glass chamber saturated with the mobile phase and the chromatoplate development for two times with the same mobile phase to get good resolution of phytochemical contents. The optimized chamber saturation time for mobile phase was 30 min at room temperature [(25±2) ^{o}C]. The developed plate was dried at room temperature in air to evaporate solvents from the plate. The plate was kept in photo-documentation chamber (CAMAG REPROSTAR 3) and captured the images under White light, UV light at 254 and 366 nm. Densitometric scanning was performed on Camag TLC scanner III and operated by CATS software (V 3.15, Camag).

Preliminary Phytochemical screeningfor identification of plant constituents

The methanolic extract of leaves of *Artocarpus hirsutus* Lam.**(MELAH)** obtained was subjected to preliminary phytochemical screening for the detection of various plant constituents.

Table.4: Preliminary Phytochemical Screening

Test for Carbohydrates			
S.No.	**Test**	**Observation**	**Inference**
1.	**Molish's test** 2-3ml of MELAH, add few drops of α-napthol solution in alcohol, shaken and added concentrated H_2SO_4 from sides of the tube	Violet ring at the junction of two liquids	Presence of carbohydrates
2.	**Fehling's test** 1ml Fehling's A& Fehling's B solutions was mixed and boiled for one minute. Add equal volume of test solution. Heated in boiling bath for 5-10min	A yellow, then brickred precipitate	Presence of Reducing sugars
3.	**Benedict's test** Equal volume of Benedict's reagent and test solution in test tube were mixed. Heated in boiling water for 5min	Solution may Appear yellow, green or red	Presence of Reducing sugars
4.	**Tannic acid test** Mix 20% tannic acid with test solution	White precipitate	Presence of starch
Test for Proteins			
1.	**Biurret test** To 3ml of test solution add 4% of NaOH and few drops of 1% $CuSO_4$ solution	Violet or pink colour	Presence of Protein
2.	**Xanthoprotein test** To 3ml of test solution, add 1ml of Conc. H_2SO_4	White precipitate	Presence of Protein
3.	**Millon's test** To 3ml of test solution add 5ml of	White precipitate	

	Millon's reagent	on warming turns brick red	Presence of Protein
Test for Amino acids			
1.	**Ninhydrin test** Heat 3ml test solution and 3 drops of 5 % Ninhydrin solution in boiling water bath for 10min	Purple or bluish colour	Presence of Amino acids
2.	Heat 3ml of test solution with Millon's reagent	Dark red colour	Presence of Amino acids (Tyrosine)
Test for Fats and Oils			
1.	Place a drop of MELAH on glass slide. Add a drop of Sudan Red III reagent. After 2min, wash with 50% alcohol. Mount in glycerine and observe under microscope	Oil globules appear red	Presence of fats and oils

Test for Alkaloids (To MELAH add dil. Hcl, shake well and filter. With the filtrate perform the following test)			
1.	**Dragendroff's test** To 2-3ml filtrate, add few drops Dragendroff's reagent	Orange brown precipitate is formed	Presence of alkaloids
2.	**Mayer's test** 2-3ml filtrate, add few drops of Mayer's reagent	Formation of precipitate	Presence of alkaloids
3.	**Hager's test** 2-3ml filtrate, add few drops of Hager's reagent	Yellow precipitate	Presence of alkaloids
Test for Steroid			
1.	**Salkowski reaction** To 2ml of test solution, add 2ml chloroform and 2ml Conc. H_2SO_4, shake well	Chloroform layer appears red and acid layer shows greenish yellow fluorescence	Presence of Steroid
2.	**Liebermann's test** Mix 3ml test solution with 3ml acetic anhydride. Heat and cool. Add few drops of Conc. H_2SO_4	Blue colour appears	Presence of Steroid

Test for Flavanoids			
1.	**Shinoda test** To the test solution, add 5ml 95% ethanol, few drops of Conc. HCl and 0.5g magnesium turnings	Pink colour observed	Presence of Flavanoids
2.	To small quantity of test solution add lead acetate solution	Yellow coloured precipitate is formed	Presence of Flavanoids

Test for Glycosides			
1.	**Legal's test** To aqueous test solution, add 1ml pyridine and 1ml sodium nitropruside	Pink to red colour appears	Presence of Glycosides
2.	**Keller-Killiani test** To 2ml of test solution, add glacial acetic acid, one drop 5% $FeCl_3$ and Conc. H_2SO_4	Reddish brown colour appears at the junction of the two liquid layers and upper layer appears bluish green	Presence of Glycosides
3.	**Foam test** The test solution was shaken vigorously	Persistent foam was observed	Presence of Glycosides
Test for Tannins and Phenolic Compounds			
1.	To the test solution, add 5% $FeCl_3$	Deep blue-black colour	Tannins/phenolic compounds
2.	To the test solution, add bromine water	Discoloration of bromine water	
3.	To the test solution, add potassium dichromate	Red precipitate	

Animal Experimentation

Pharmacological evaluation of methanolic extract of *Artocarpus hirsutus* Lam.was carried out in the Department of Pharmacology, Periyar College of Pharmaceutical Sciences, Tiruchirappalli, Tamilnadu, India. Animal facility of this institute is approved by CPCSEA, NewDelhi. The experimental protocols for the antiulcer,anticonvulsant and antidiarrhoeal activities have been approved by the Insititutional Animal Ethics Committee (IAEC) and conducted according to the guidelines of Indian National Sciences Academy for the use and care of experimental animals.IAEC approved this proposal with approval number PCP/IAEC/002/2013. The animals were maintained at a well ventilated, temperature controlled $30^{o}C \pm 1^{o}C$ animal room for 7days prior to the experimental period and provided with food and water *ad libitum*. The animals were acclimatized to laboratory conditions before the test. Each animal was used only once.

Toxicity studies

1) Acute oral toxicity - Guideline number 423[75]

The set out in this guideline is a stepwise procedure and depending on the mortality and/or the morbid status of the animals, an average of 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance.

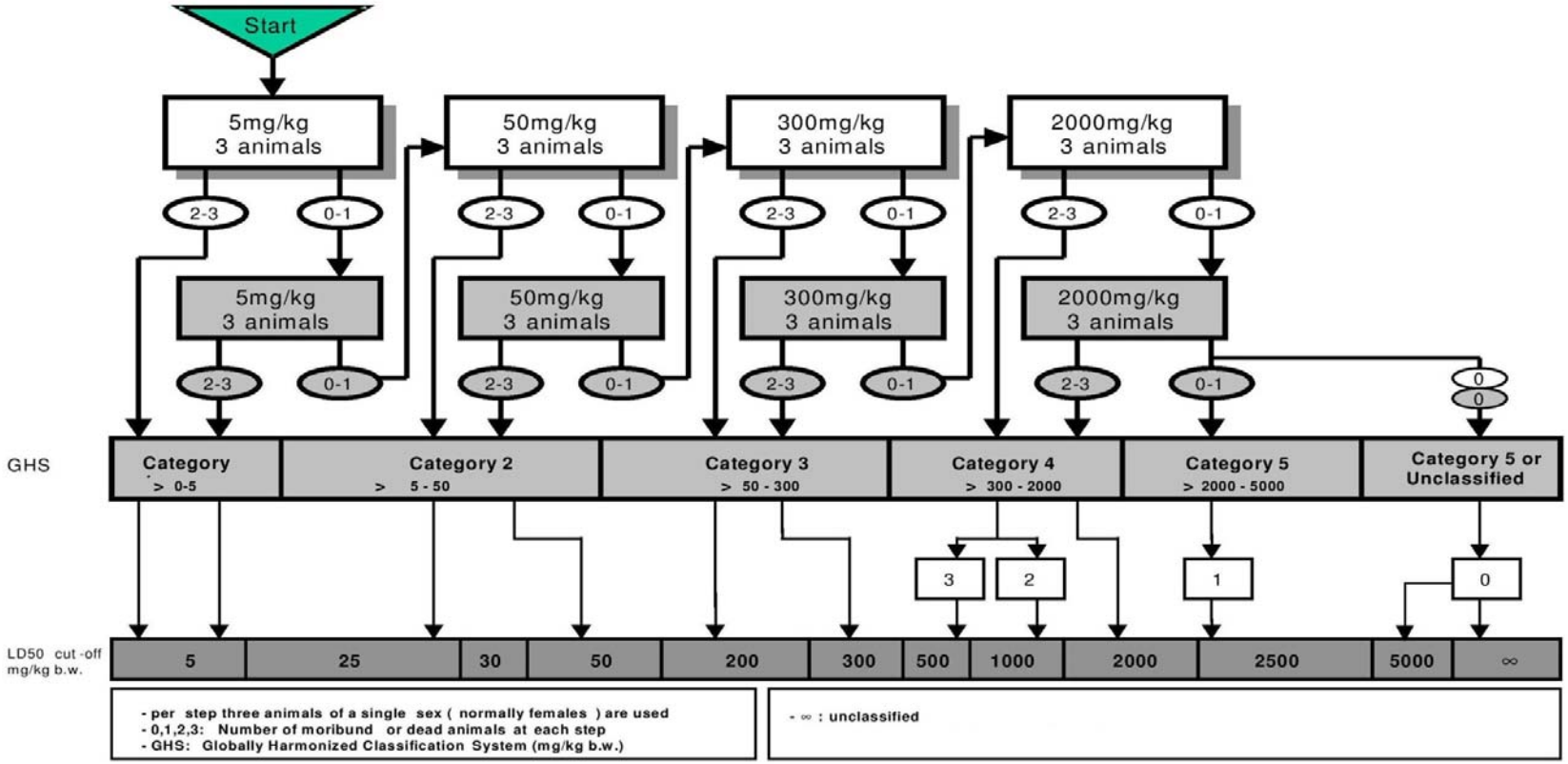
The test substance was administered orally to a group of experimental animals at one of the defined doses. The substance was tested using a stepwise procedure using three animals of a single sex (normally females) per step. Absence or presence of compound related mortality of the animals dosed at one step determined the next step i.e.

- no further testing is needed
- dosing of three additional animals, with the same dose
- dosing of three additional animals at the next higher or the next lower dose level

Healthy young female adult animals were used. The test substance was administered in a single dose by gavage using a stomach tube. The dose level to be used as the starting dose was selected from one of four fixed levels, 5, 50, 300 and 2000mg/kg body weight. The starting dose level should be that which is most likely to produce mortality in some of the dosed animals. The time interval between treatment groups was determined by the onset, duration and severity of toxic signs. Treatment of animals at the next dose should be delayed until one is confident of survival of the previously dosed animals. Animals were observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours with special attention given during the first 4 hours and daily thereafter for a total of 14 days.

Observations should include changes in skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous systems, and somatomotor activity and behavior pattern. Attention should be directed to observations of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma. In addition behavioral changes, biochemical parameters and histopathological studies were also observed.

Figure.4 Guideline 423 for Acute oral toxicity



Test procedure with a starting dose of 5mg/kg body weight

Pharmacological Evaluation

1) Evaluation of antiulcer activity of MELAH

a) Alcohol induced ulcer[49,54,55]

Materials

Animals

Adult Wistar albino rats weighing 200-220 gmwere used for the study. In the laboratory, rats were fed with standard rat pellet diet (Lipton India Ltd, Bangalore) and water *ad libitum*. They were housed in Tarson's polypropylene cages with metal grill tops and acclimated to the laboratory conditions.

Drugs

The methanolic extract of *Artocarpus hirsutus* was administered at doses of200mg/kg and 400 mg/kg, p.o.Lansaprazole was used as standard drug at a dose of 8 mg/kg, p.o. The agent used for inducing ulcer was 1ml/200 gmof alcohol, p.o.(0.1N HCl and 80% ethanol).

Experimental Design

Alcohol induced ulcer model was used to assess the antiulcer activity in albino rats following procedures as under.

The animals are fasted for 24 hours with free access to water. Animals were divided into 5 groups containing 6 animals in each.The first group of animals were administered 1% normal saline 1ml/100gm, p.o. which will serve as negative control. Group II animals were treated with alcohol,1ml/200gm, p.o. which served as positive control. Group III animals were treated with Lansaprazole 8mg/kg, p.o. which served as positive control. Group IV &V animals was pretreated with MELAH at doses of 200 mg/kg, p.o. and 400 mg/kg, p.o.. 1 hr later 1ml/200gmof alcohol (0.1N HCl and 80% ethanol) was administered p.o. to each animal.

Animals was sacrificed 1 hr after alcohol administration, stomachs were isolated and cut open along the greater curvature and pinned on the soft board. The ulcer index was measured. The number of ulcers of was noted and severity of ulcers were scored with help of hand lens .

Statistical analysis

Data are presented as Mean ± SEM. The data was analysed using one way analysis of variance (ANOVA). The statistical significance of the difference of the means was evaluated by Dunnett's multiple comparision test.

b) Aspirin induced ulcer[49,57,62]

Materials

Animals

Adult Wistar albino rats weighing 200-220 gmwere used for the study. In the laboratory, rats were fed with standard rat pellet diet (Lipton India Ltd, Bangalore) and water *ad libitum*. They were housed in Tarson's polypropylene cages with metal grill tops and acclimated to the laboratory conditions.

Drugs

The methanolic extract of *Artocarpus hirsutus* was administered at doses of 200 mg/kg, p.o. and 400 mg/kg, p.o.Lansaprazole was used as standard drug at a dose of 8mg/kg, p.o.The agent used for inducing ulcer was aspirin at dose of 200 mg/kg, p.o.

Experimental Design

Aspirin induced ulcer model was used to assess the antiulcer activity in albino rats following procedures as under.

The animals are fasted for 24 hours with free access to water. Animals were divided into five groups of six animals . The first group of animals was administered 1% normal saline 1ml/100gm, p.o.which served as negative control.

Group II animals were treated with aspirin 200mg/kg, p.o. which was served as positive control. Group III animals were treated with Lansaparazole 8mg/kg, p.o.which was served as standard. Group IV &V animals was treated with MELAH 200mg/kg,p.o. 400mg/kg, p.o. The test drugs are administered orally in 2% gum acacia solution 30 min prior to aspirin at dose of 200mg/kg, p.o. Four hours later the rats were sacrificed by using anaesthetic ether and their stomachs will be dissected . The ulcer index was measured. The number of ulcers of was noted and severity of ulcers were scored microscopically with help of hand lens .

Statistical analysis

Data are presented as Mean ± SEM. The data was analysed using one way analysis of variance (ANOVA). The statistical significance of the difference of the means was evaluated by Dunnett's multiple comparision test.

2) **Evaluation of anticonvulsant activity of MELAH**

Anti-convulsant activity of MELAH

a) Maximal electroshock (MES) induced convulsions[50,56,59]

Materials

Animals

Adult Wistar albino rats weighing 200-220g were used for the study. In the laboratory, rats were fed with standard rat pellet diet (Lipton India Ltd, Bangalore) and water *ad libitum*. They were housed in Tarson's polypropylene cages with metal grill tops and acclimated to the laboratory conditions.

Drugs

The methanolic extract of leaves of *Artocarpus hirsutus* was administered at doses of 200 mg/kg, p.o. and 400 mg/kg, p.o. Phenytoin was used as standard drug at a dose of 25 mg/kgp.o.

Experimental Design

The anticonvulsant activity of the extract was studied in the normal animals. The convulsion were induced by Maximal electroshock seizure model by delivering

electroshock of 150mA for 0.2 seconds by means of an electroconvulsiometer through a pair of corneal electrodes.

Methodology

The animals were divided into 4 groups with each group containing six animals. Maximal electroshock seizure model was used to evaluate the anticonvulsant activity of MELAH. Seizures were induced in rats by delivering electroshock of 150 mA for 0.2 sec by means of an electroconvulsiometer through a pair of corneal electrodes. Group I were treated as control, Group II were treated as standard group and received phenytoin 25mg/ kg, p.o . Group III were received MELAH 200mg/kg, p.o. and Group IV were received MELAH 400 mg/kg, p.o. and tested after 60 minutes for MES induced seizure response. Duration of various phases of epileptic attacks were recorded and compared with the control and phenytoin group.

Statistical analysis

Data are presented as Mean ± SEM. The data was analysed using one way analysis of variance (ANOVA). The statistical significance of the difference of the means was evaluated by Dunnett's multiple comparision test.

3) Evaluation of Anti diahorreal activity of MELAH

a) Castor oil induced diarrhoea[52,53]

Materials

Animals

Female Wistar albino rats weighing 200-220 gm were used for the study. In the laboratory, rats were fed with standard rat pellet diet (Lipton India Ltd, Bangalore) and water *ad libitum*. They were housed in Tarson's polypropylene cages with metal grill tops and acclimated to the laboratory conditions.

Drugs

The methanolic extract of leaves of *Artocarpus hirsutus* was administered at a doses of 200 mg/kg,p.o. and 400 mg/kg, p.o. Loperamide was used as standard drug at a dose of 3mg/kg, p.o. The agent used for inducing diarrhoea was Castor oil 1ml/kg, p.o.

Experimental Design

The antidiahorreal effect of methanolic extract of *Artocarpus hirsutus* the was studied in animals with experimentally induced diarrhoea.

The diarrhoea was induced by oral administration of 1ml/kg castor oil, p.o. The parameters observed were frequency of diarrhoeal output, number of faeces drops and weight of faeces.

Methodology

Female Wistar rats weighing 210-230 gm were used after overnight food deprivation. For the experiment, the rats were housed in individual cages with no access to drinking water. Fasted rats were divided into five groups of six animals each.

Group I served as control
Group II treated as diarrhoeal Control and received Castor oil 1ml/kg, p.o.
Group III were treated with Loperamide - 3mg/kg, p.o.
Group IV received MELAH at a dose of 200 mg /kg, p.o.
Group V received MELAH at a dose of 400mg /kg, p.o.

One hour after dosage, 1 ml of castor oil was administered orally to all the groups to induce diarrhoea. Stools were collected on non-wetting paper sheets of uniform weight up to 4 hrs after administration of the castor oil. Frequency of diarrhoeal output, number of faeces drops and weight of faeces were recorded.

The values are expressed as ± standard error of the mean. Test of significance was analyzed by One way ANOVA followed by Dunnett's test.

6. RESULTS AND DISCUSSION

Preliminary Phytochemical screening

As a part of the preclinical study, the methanolic extract of leaves of *Artocarpus hirsutus* Lam.**(MELAH)** was subjected to qualitative chemical test and confirmed the presence of carbohydrates, alkaloids, steroids, flavanoids, saponins, glycosides, tannins and phenolic compounds shown in **Table.5**

Table.5: Preliminary Phytochemical screening

S.No	Plant Constituents	MELAH
1.	Carbohydrates	+
2.	Proteins	+
3.	Amino acid	+
4.	Fat and Oil	-
5.	Alkaloids	+
6.	Steroids	+
7.	Flavonoids	++
8.	Tannins and Phenolic compounds	+
9.	Saponins	+
10.	Glycosides	+

(+) = Presence, (-) = Absence

ANALYTICAL DETERMINATION

1. HPTLC analysis

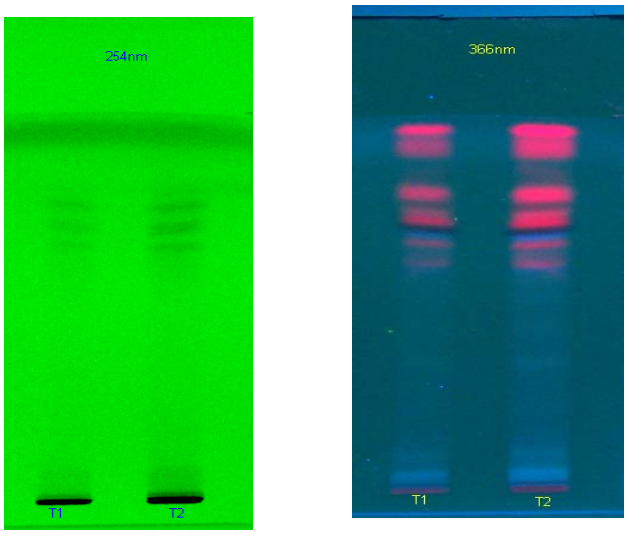
The chromatograms shown in **Fig.4** indicate that the sample constituents were clearly separated without any tailing and diffusenses. The investigation of the intense bands obtained from HPTLC profile showed unknown compounds predominantly as shown in **Tables 6and 7.** A peak display at 5 µl **(Fig.6),** 10 µl **(Fig.7)** a 3D display **(Fig. 5)** of the **MELAH** were shown. The peak corresponding to R_f value of 0.67 depicts that it may be presence of flavanone[86].

Optimized Chromatographic conditions

Stationary Phase	:	Merck HPTLC plates coated with Silica Gel 60 F_{254} of 0.2 mm thickness
Mobile Phase	:	Toulene: Ethyl Acetate: Formic acid (5:4:1)
Sample Applicator	:	Camag linomat V automatic applicator
Scanner	:	Camag Scanner
Syringe	:	Hamilton syringe (100 µl)
Wavelength	:	254 nm

Fig.5: PHOTO DOCUMENTATION UNDER UV

AT 254 nm AT 366 nm



T1 T2 T1 T2

TLC DETAILS

Track T1-5µl of Methanolic Ext
Track T2- 10 µl of Methanolic Ext

Fig. 6: Chromatogram of MELAH 3D display at 254 nm

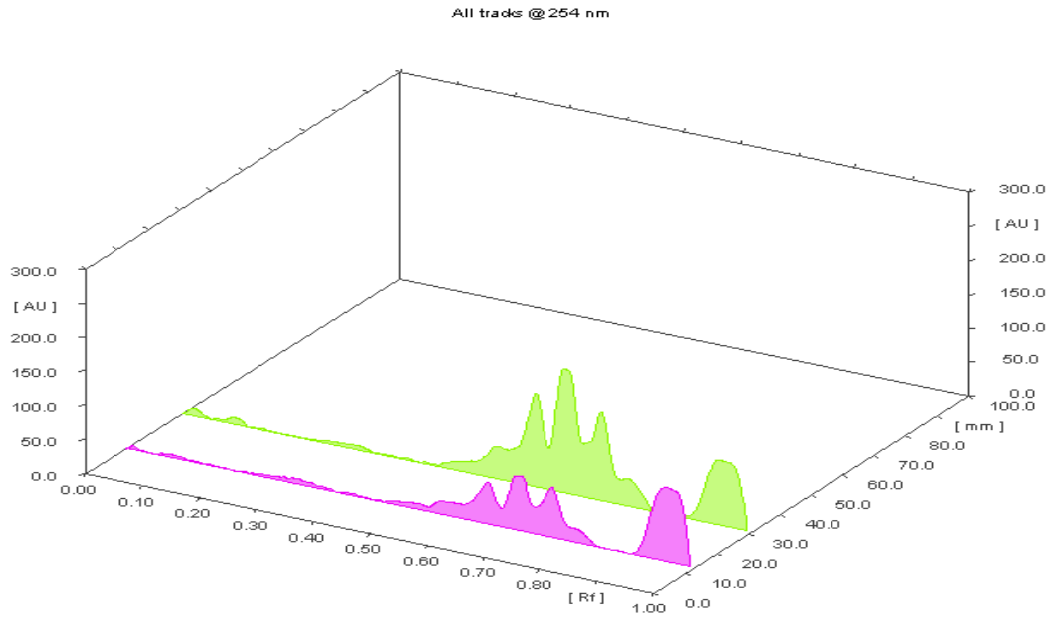


Fig.7: PEAK DISPLAY (5µl of Methanolic Extract)

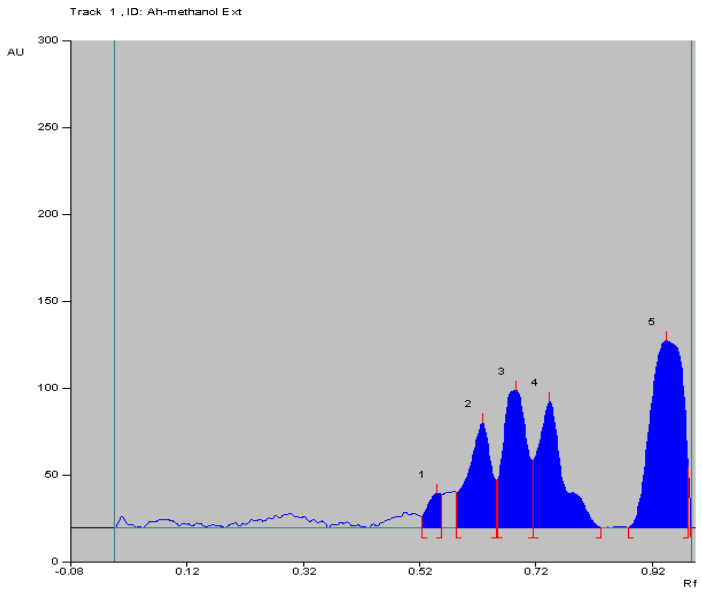


Table.6: Chromatogram Data for (5µl Methanolic extract)

Peak	Start R_f	Start Height	Max R_f	Max Height	Height %	End R_f	End Height	Area	Area %	Assigned Substance
1	0.53	6.7	0.56	19.6	5.78	0.56	19.2	344.9	3.06	Unknown*
2	0.59	20.4	0.63	60.2	17.71	0.66	27.1	1766.1	15.66	Unknown*
3	0.66	27.5	0.69	79.3	23.33	0.72	38.9	2366.5	20.98	Unknown*
4	0.72	39.1	0.75	72.9	21.45	0.84	0.2	2333.2	20.69	Unknown*
5	0.88	0.1	0.95	107.8	31.74	0.99	34.8	4466.0	39.61	Unknown*

Fig.8: PEAK DISPLAY (10µl of Methanolic Extract)

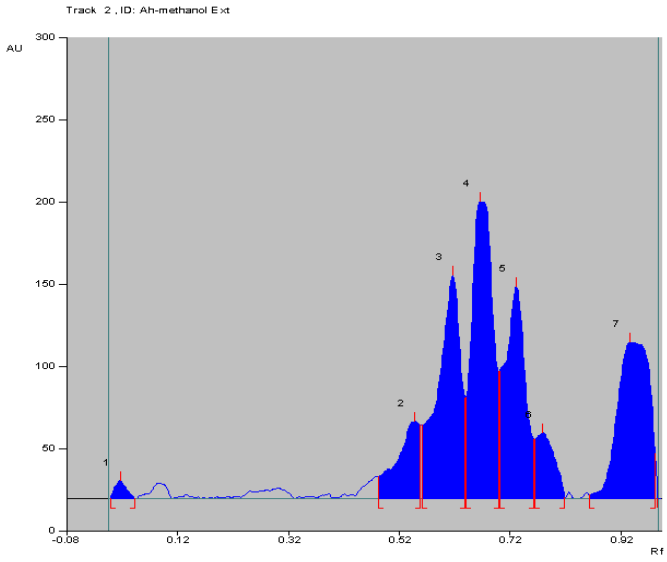


Table.7: Chromatogram Data for (10µl of Methanolic extract)

Peak	Start R_f	Start Height	Max R_f	Max Height	Height %	End R_f	End Height	Area	Area %	Assigned Substance
1	0.0	0.1	0.02	11.0	1.34	0.04	1.7	139.3	0.44	Unknown*
2	0.10	10.8	0.17	188.6	22.86	0.22	2.6	5891.9	18.06	Unknown*
3	0.27	4.7	0.37	72.7	8.80	0.41	23.2	2654.3	8.42	Unknown*
4	0.41	23.3	0.48	64.5	7.81	0.51	50.6	2880.6	9.14	Unknown*
5	0.51	50.7	0.56	73.0	8.85	0.58	65.4	2960.1	9.39	Unknown*
6	0.59	65.4	0.63	116.5	14.11	0.67	60.0	4499.2	14.27	Unknown*
7	0.67	60.1	0.74	87.8	10.64	0.77	66.1	4629.3	14.69	Unknown*

TOXICITY STUDIES

1) Acute oral toxicity: Guideline number - 423

In acute oral toxicity studies, Methanolic extract of leaves of *Artocarpus hirsutus* (MELAH) did not produce mortality at a dose of 2000mg/kg body weight in rats and hence1/10th ofLD_{50}(i.e.) 200mg/kg was considered as the dose level for further pharmacological screening. The parameters observed were behavioral changes, biochemical parameters, histopathological studies and mortality.

BEHAVIOURAL CHANGES

Behavioural changes observed were death, abnormal gait, aggression, akinesia, altered fear, altered muscle tone, altered respiration, analgesia, body temperature, catalepsy, convulsions, excitation, fore paw treading, jumping, loss of balance, motor in-coordination, sedation, stereotypy, straub tail, tremor, writhing, altered reactivity to touch, defaecation/diarrhoea, head movements, lacrimation, loss of corneal reflux, loss of righting reflux, loss of traction, miosis/mydriasis, salivation and scratching. Among the behavioural parameters observed the animal showed positive response for altered fear, fore paw treading, motor incoordination and sedation. **(Table 8)**.

Table.8: Effect of MELAH on Behavioural changes in Rats

S.No.	Symptoms	MELAH (2000 mg/kg)
1.	Death	-
Central Nervous System		
2.	Abnormal gait	-
3.	Aggression	-
4.	Akinesia	-
5.	Altered fear	+
6.	Altered muscle tone	-
7.	Altered respiration	-
8.	Analgesia	-
9.	Body temperature	-
10.	Catalepsy	-
11.	Convulsions	-
12.	Excitation	-
13.	Fore paw treading	+
14.	Jumping	-
15.	Loss of balance	-
16.	Motor in-coordination	+
17.	Sedation	+
18.	Stereotypy	-
19.	Straub tail	-
20.	Tremor	-
21.	Writhing	-
Autonomous Nervous System		
22.	Altered reactivity to touch	-
23.	Defaecation/Diarrhoea	-
24.	Head movements	-
25.	Lacrimation	-
26.	Loss of corneal reflex	-
27.	Loss of righting reflex	-
28.	Loss of traction	-
29.	Miosis/Mydriasis	-
30.	Salivation	-
31.	Scratching	-

BIOCHEMICAL PARAMETERS

The biochemical parameters observed in animals treated with 2000 mg/kg of MELAH were albumin, globulin, blood urea,glucose, SGOT, SGPT, total cholesterol and uric acid. All the biochemical parameters were in normal range. The increase in level of sugar, SGOT,SGPT, ALP and blood urea were observed. **(Table 9)**.

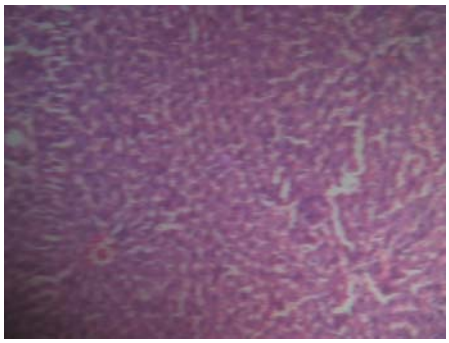
Table.9: Effect of MELAH on Biochemical parameters in Rats

S.No.	Test	Result
		MELAH (2000mg/kg)
1.	Albumin (g/dl)	3.2
2.	Blood urea (mg/dl)	230
3.	Glucose (mg/dl)	87
4.	SGOT (U/l)	810
5.	SGPT (U/l)	186
6.	ALP	1151
7.	Total Cholestrol (mg/dl)	67
8.	Globulin	4.2

HISTOPATHOLOGICAL STUDIES

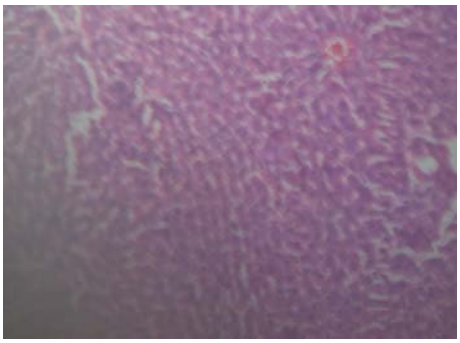
T.S of Liver

Fig.9



CONTROL

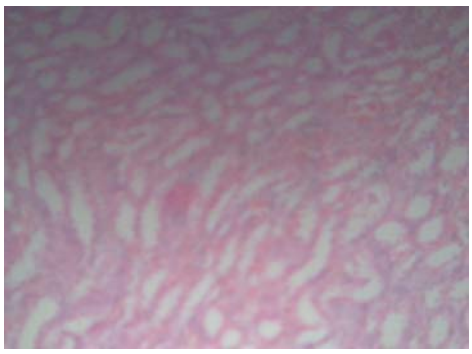
Fig.10



MELAH TREATED

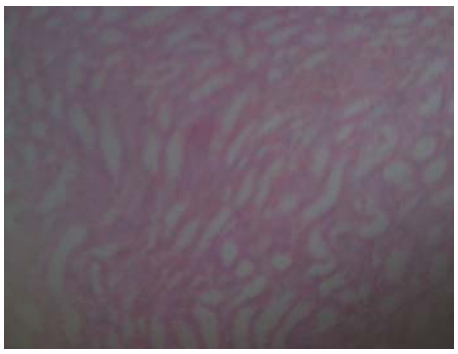
T.S. of Kidney

Fig.11



CONTROL

Fig.12



MELAH TREATED

Table.10: Effect of MELAH on T.S of Liver and Kidney

S.No.	T.S. of Organ	Report
1.	Liver	The tissue shows dilated central and portal traids and shows preserved and normal architechture.
2.	Kidney	Glomeruli and tubules were normal and shows normal histology

PHARMACOLOGICAL EVALUATION

A. Antiulcer activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* (MELAH)

i) Alcohol induced ulcer

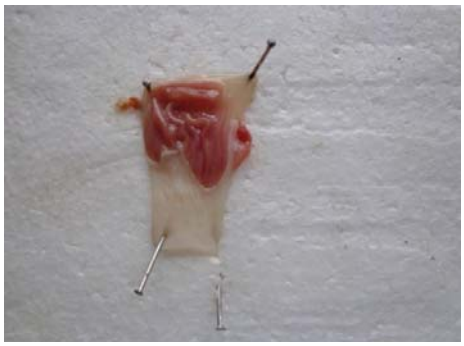
Results of antiulcer activity of MELAH on alcohol induced ulcer are shown and presented in Fig.12, Fig.13 and Table.11 The results showed significant increase in ulcer score in alcohol control group compared to normal control. The ulcer score decreased after treatment with MELAH ($P<0.0001$) and lansaprazole there by decreasing the damage to gastric mucosa of stomach and formation of Hcl secretion.

Antiulcer activity of MELAH was determined by alcohol induced ulcer. Stomach being the principal organ of ulcer, its administration to the experimental animals for 24 hours fasting resulted in various degree of ulcers.

Alcohol increases the risk of ulcer by damaging the gastric mucosa of the stomach and increasing the gastric Hcl of the stomach.The genesis of alcohol induced gastric lesions is multifactorial with the depletion of gastric wall mucous content as one of the involved factors. It is also associated with significant production of free radicals, leading to an increased oxidative stress and damage to the cell and cell membrane. The pepsin may have a role in the etiology of gastric ulceration and cancer.This suggests that inhibitors of acid secretion may prevent ulceration not only by the removal of acid but also by inactivation of pepsin following the subsequent rise in gastric pH.Therefore acid secretion may not have to be suppressed to prevent the development of gastric ulcers since the inhibition of pepsin activity alone may be sufficient to heal the ulcers and theside effects of suppressing acid secretion can be avoided. Proteolytic activity of pepsin as the primary aggressor in gastric mucosal ulceration[57,58] .

Fig.13: Photos of Antiulcer activity of MELAHtreated rat in Alcohol induced ulcer model

CONTROL



ULCER CONTROL

LANSAPRAZOLE (8 mg/kg)

MELAH (200 mg/kg)

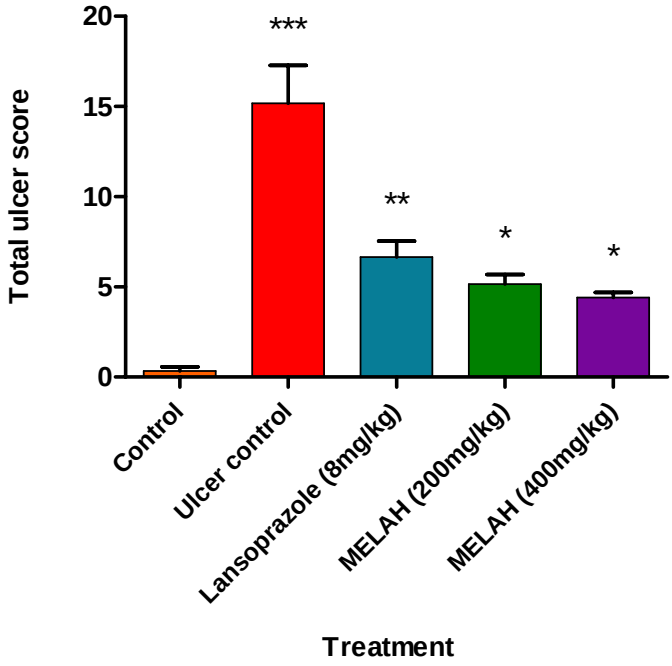
MELAH (400 mg/kg)

Table.11: Effect of MELAH on Alcohol induced ulcer in Rats

Treatment	Ulcer Index					Total Score Mean ± SEM	% Inhibition
	Red coloured stomach	Spot ulcer	Haemorraghic streaks	Ulcers<3mm	Ulcers>3mm		
Control Distilled water, 1ml p.o.	1	1	-	-	-	0.333 ± 0.247	-
Ulcer control Alcohol (1 ml/ 200 gm, p.o)	3	44	36	-	6	15.167 ± 2.108	-
Alcohol (1 ml/ 200 gm,p.o) + Lansaprazole (8mg/kg,p.o)	-	25	13.5	2	-	6.667 ± 0.872**	55.49
Alcohol (1 ml/ 200 gm,p.o.) + MELAH (200mg/kg, p.o)	-	26	3	2	-	5.16 ± 0.527*	65.93
Alcohol (1 ml/ 200 gm,p.o.) + MELAH (400mg/kg, p.o)	-	25	1.5	2	-	4.417 ± 0.271*	70.87

n = 6. Total Score Values are expressed as ± S.E.M.***P < 0.001, ns P > 0.05 Vs Control (One way ANOVA followed by Dunnett's test)

Fig. 14 Effect of MELAH on Alcohol induced ulcer in Rats



ii) Aspirin induced ulcer

Results of antiulcer activity of MELAH on asprin induced ulcer are presented in **Fig.14, Fig.15** and **Table.12** The results showed significant increase in ulcer score in aspirin control group compared to normal control. The ulcer score decreased after treatment with MELAH ($P<0.0001$) and lansaprazole there by decreasing the damage to gastric mucosa of stomach.

Antiulcer activity of MELAH was determined by aspirin induced ulcer. Aspirin causes mucosal damage by interfering with prostaglandin synthesis, increasing acid secretion, and back diffusion of H+ ions. In stomach, prostaglandins play a vital protective role by stimulating secretion of HCO^{-3} and mucous, maintaining mucosal blood flow and regulating mucosal cell turnover, and repair.

Thus the suppression of prostaglandin synthesis by NSAIDs results in increased susceptibility to mucosal injury and gastro duodenal ulceration ROS (reactive oxygen species) plays an important role in pathogenesis of mucosal damage caused by aspirin besides inhibition of COX enzymes[49,63].

The present study observed that reduced aspirin induced ulcers suggesting possible involvement of prostaglandin and mucus.These effects ultimately break down gastric mucosal barriers. Pretreatment of rat with MELAH ($P<0.0001$) and subsequent protection from gastric mucosal damage induced by aspirin reflected a clear tendency to enhance gastric mucosal protective mechanism.

Fig.15: Photos of Antiulcer activity of MELAH treated rat in Aspirin induced ulcer model

CONTROL

ULCER CONTROL

LANSAPRAZOLE (8 mg/kg)

MELAH (200 mg/kg)

MELAH (400 mg/kg)

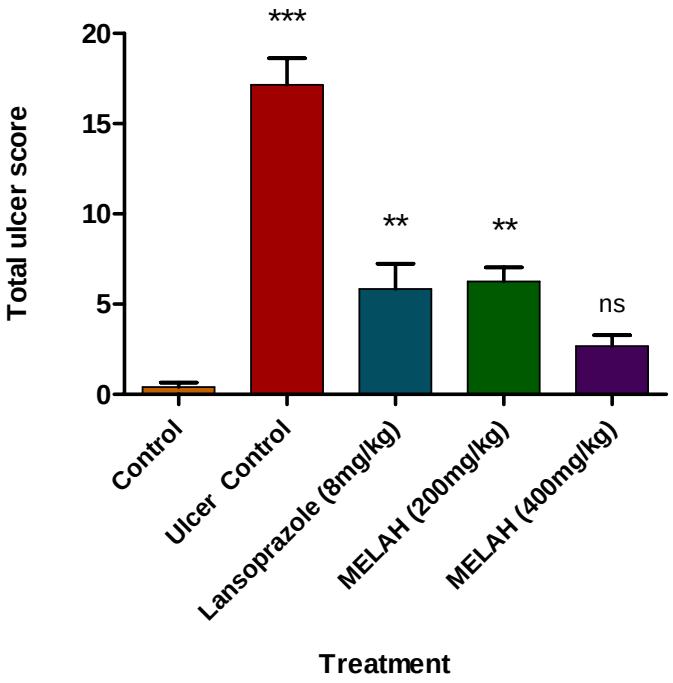
Table.12: Effect of MELAH on Aspirin induced ulcer in Rats

Treatment	Ulcer Index					Total Score Mean ± SEM	% Inhibition
	Red coloured stomach	Spot ulcer	Haemorraghic streaks	Ulcers<3mm	Ulcers>3mm		
Control Distilledwater 1 ml, p.o.	1	1.5	-	-	-	0.417 ± 0.239	-
Ulcer control Aspirin 200 mg/kg, p.o.	3	22	66	6	6	17.167 ± 1.459***	-
Aspirin 200 mg/kg, p.o. + Lansaprazole 8mg/kg,p.o.	-	7	18	-	-	5.833 ± 1.406**	66.21
Aspirin 200 mg/kg, p.o. + MELAH 200mg/kg, p.o.	-	28	7.5	2	-	6.250 ± 0.793**	63.59
Aspirin 200 mg/kg, p.o. + MELAH 400mg/kg, p.o	-	13	3	-	-	2.667 ± 0.601ns	84.46

n = 6. Total Score Values are expressed as ± S.E.M.***P < 0.001, ns P > 0.05 Vs Control

(One way ANOVA followed by Dunnett's test)

Fig.16 Effect of MELAH on Aspirin induced ulcer in Rats



B. Anticonvulsant activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* (MELAH)

i) MES Induced convulsions[51,60]

Results of anticonvulsant activity of MELAH on MES induced convulsions are presented in **Fig.16, Fig.17, Fig.18 and Fig.19** and **Table.13.** The results showed significant reduction in compared to normal control. The tonic extension phase decreased after treatment with MELAH($P<0.0001$) and phenytoin there by reducing the seizure spread.

Anticonvulsant activity of MELAH was determined by MES induced convulsions. Antiepileptic drugs that block MES induced tonic extension act by blocking seizure spread. Moreover MES induced tonic extension can be prevented either by drugs that inhibit voltage dependent Na^+ channels, such as phenytoin, valproate, felbamate and lamotrigene.

The MES test identifies agents with activity against generalized tonic clonic seizures using clinically established antiepileptic drugs. In addition to identifying drug activity against generalized tonic-clonic seizures, it has often been proposed that the maximal electroshock test predicts anticonvulsant drug effective against partial seizures[51,60].

Table.13: Effect of MELAH on various phases of MES- induced convulsions

Treatment	Time(s) in various phase of convulsion (mean±SEM)					
	Flexion	Extension	% Inhibition	Clonus	Stupor	Recovery (R) or death (D)
Normal saline 1 ml/kg, p.o	4.000 ± 0.258	16.000 ± 0.577	-	240.000 ± 0.577	360.000 ± 0.577	Recovered
Standard Phenytoin 25 mg/kg, p.o.	0.000 ± 0.00***	0.000 ± 0.000	100	240.00 ± 0.577	300.00 ± 0.577***	Recovered
MELAH 200 mg/kg, p.o.	2.000 ± 0.365***	10.000 ± 0.365***	37.5	160.000 ± 0.577***	180.000 ± 0.577***	Recovered
MELAH 400 mg/kg, p.o.	1.000 ± 0.000***	4.000 ± 0.258***	75	80.000 ± 0.577***	200.000 ± 0.931***	Recovered

n = 6. Values are expressed as ± S.E.M.***P < 0.001, ns P > 0.05Vs Control

(One way ANOVA followed by Dunnett's test).

Fig. 17 Effect of MELAH on Flexor Phase of MES induced convulsions in Rats

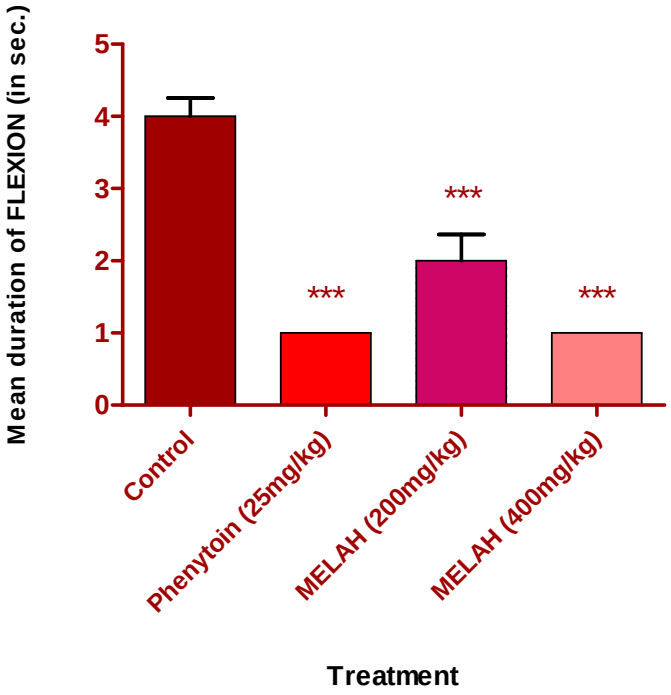


Fig. 18 Effect of MELAH on Extensor Phase of MES induced convulsions in Rats

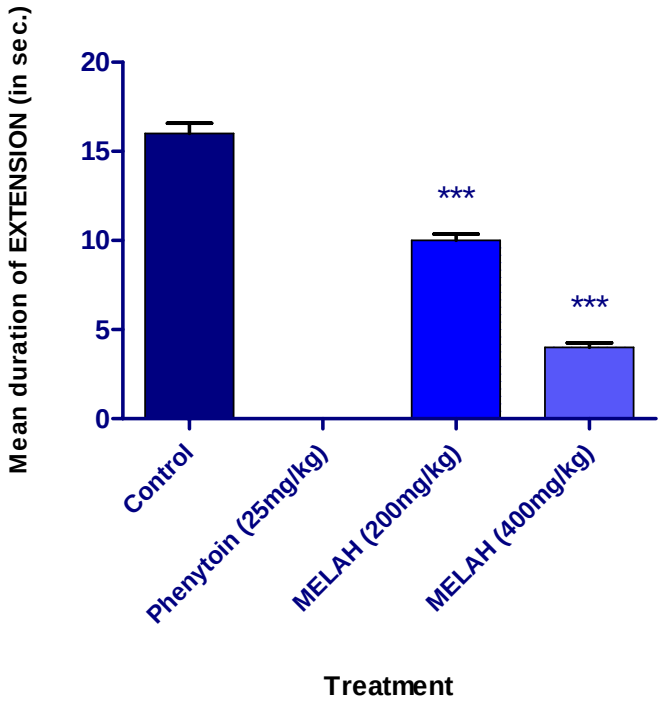


Fig. 19 Effect of MELAH on Clonus Phase of MES induced convulsions in Rats

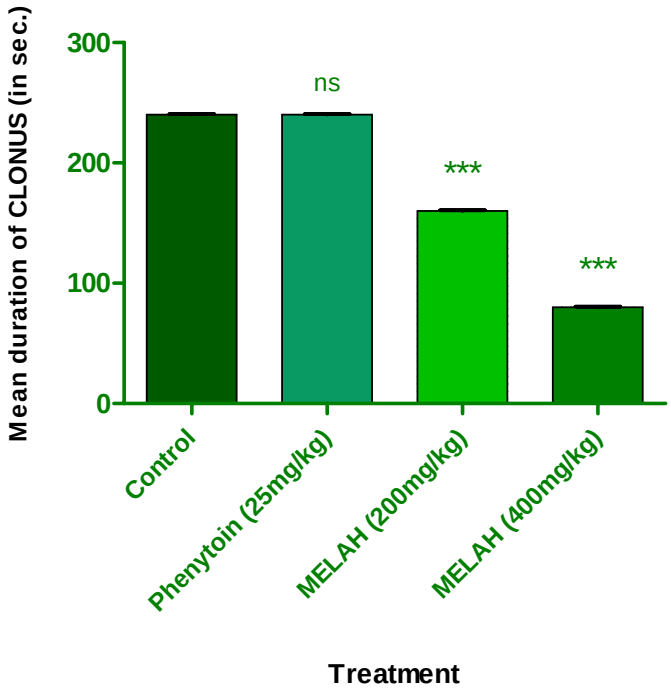
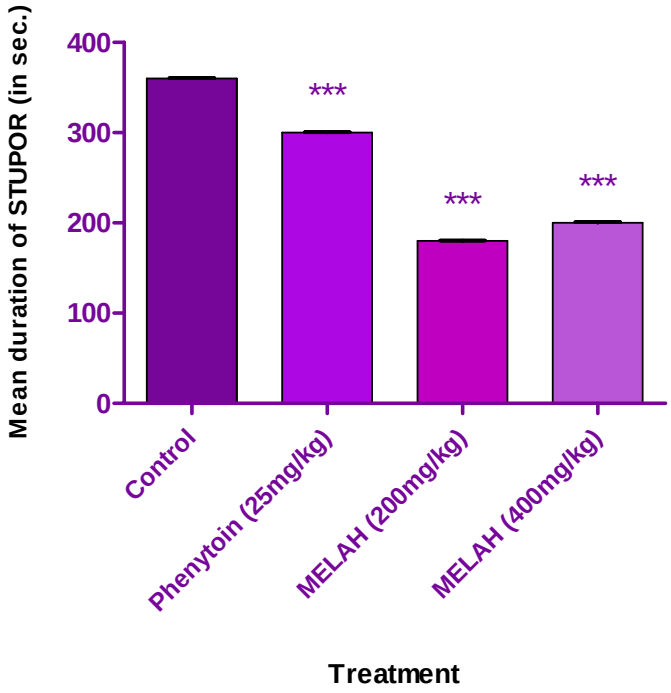


Fig. 20 Effect of MELAH onStupor Phase of MES induced convulsions in Rats



C. Anti diarrhoeal activity of Methanolic Extract of Leaves of *Artocarpus hirsutus* (MELAH)

(i) Castor oil induced diarrhoea

Results of antidiarrhoeal activity of MELAH on castor oil induced diarrhoea are shown and diarrhoeal parameters like frequency of diarrhoea, no of faecal drops and weight of the faeces for 4 hrs are presented **in Fig.20, Fig.21,** and **Fig.22** and **Table.14** The results showed significant reduction in compared to control. In this study, MELAH exhibited a significant($P<0.0001$)antidiarrhoeal activity. The results were similar to that of the standard drug loperamide 3 mg/kg. ($P<0.0001$)

Antidiarrhoeal activity of MELAH was determined by castor oil induced diarrhoea. Diarrhoea is usually considered a result of altered motility and fluid accumulation within the intestinal tract. Many antidiarrhoeal agents act by reducing the gastrointestinal motility and or the secretions. Castor oil causes diarrhoea due to its active metabolite ricinoleic acid, which stimulates peristaltic activity in the small intestine, leading to changes in the electrolyte permeability of the intestinal mucosa. Its action also stimulates the release of endogenous prostaglandin. Prostaglandin contributes to the pathophysiological functions in gastrointestinal tract[52,53] .

Table.14: Effect of MELAH on Castor oil induced diarrhoea in Rats

Treatment	Frequency of Diarrhoea (at 4 hrs)	No. of Faecal drops (at 4 hrs)	% Inhibition	Wt. of Faeces (gm) (at 4 hrs)	% Inhibition
Control Distilled water 1 ml, p.o	0.000±0.000	1.000±0.000	-	0.000±0.000	-
Diarrhoeal control Castor oil 1 ml/kg, p.o	16.667±0.494***	2.000±0.000***	-	66.000±0.632	-
Loperamide 3 mg/kg, p.o.	38.167±0.494***	0.833±0.105ns	70.38	13.667±0.441***	79.54
MELAH 200 mg/kg, p.o	24.833±0.601***	1.667±0.211ns	29.16	46.833±0.477***	29.04
MELAH 400 mg/kg, p.o	30.000±0.683***	1.167±0.105**	41.66	35.000±0.365***	46.96

n = 6. Values are expressed as ± S.E.M***P < 0.001, ns P > 0.05 Vs Control

(One way ANOVA followed by Dunnett's test)

Fig. 21 Effect of MELAH on Frequency of Diarrhoea on Castor oil induced diarrhoea in Rats

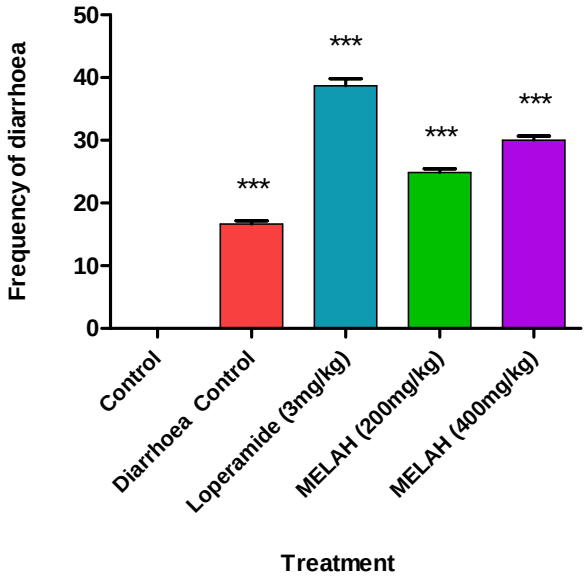


Fig. 22 Effect of MELAH on Number of Faecal drops on Castor oil induced diarrhoea in Rats

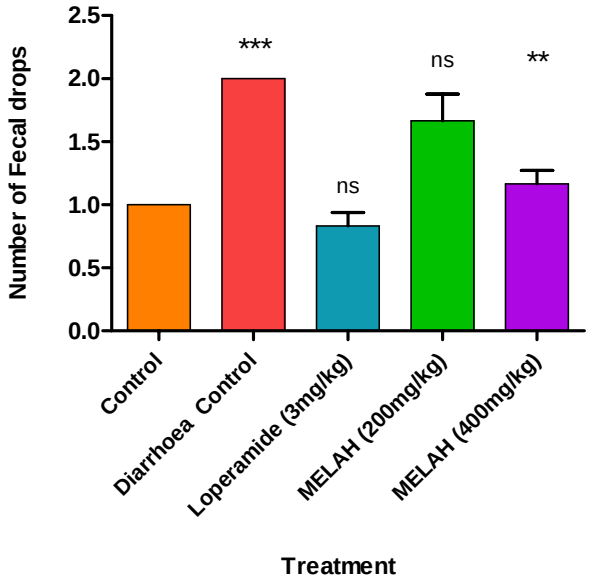
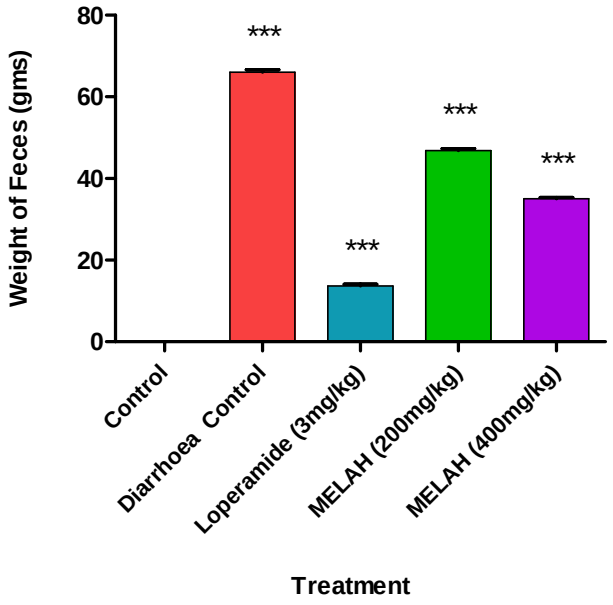


Fig. 23 Effect of MELAH on Weight of the Faces on Castor oil induced diarrhoea in Rats



7. CONCLUSION

- Presence of Flavanoids in the Methanolic extract of leaves of *Artocarpus hirsutus* Lam. was confirmed by HPTLC analysis. Though present in small quantities, it was found to produce considerable effects

- The results of the present study indicate that the Methanolic extract of leaves of *Artocarpus hirsutus* Lam. was safer at a dose level of 2000 mg/kg

- The present study indicating the presence of antiulcer effect in methanolic extract of leaves of *Artocarpus hirsutus* Lam. leaves against alcohol (70.87%) and aspirin (84.46%) induced ulcer models possibly through a direct corrosive effect on gastric epithelium, leading to mucosal damage on the glandular part of the stomach and aspirin induced gastric damage is due to direct irritant effect of aspirin on gastric mucosa, increased acid secretion and decreased mucin secretion due to inhibition of prostaglandins (PG) synthesis

- The Anticonvulsant effects of methanolic extract of the leaves of *Artocarpus hirsutus* Lam. acts against the seizures induced by MES induced convulsions. It possesses potent (75%) anticonvulsant activity in the treatment of generalized tonic clonic and partial seizures.

- From the results it is indicated that the methanolic extract of leaves of *Artocarpus hirsutus* Lam. It possess (46%) antidiarrhoeal activity by decreasing frequency of diarrhoea, number of faecal drops and weight of the faeces. However the activity was based on terms of quantitative activity elicited by standard drug.

- In future, further investigation might provide an insight to identify and characterize the exact active phytoconstituents responsible for the antiulcer, anticonvulsant and antidiarrhoeal effect and to elucidate the exact mechanism of action, which is responsible for the observed significant activity with low toxicity and better therapeutic index

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